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METABOLIC AND REFLEX INFLUENCES ON PULMONARY VASOMOTION

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DEDICATION

This thesis is dedicated to Dr. S.E. Downing under whose guidance this study was conducted and who, as a teacher and friend, has been a continuing source of inspiration.

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For Poo

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I. INTRODUCTION

The pulmonary vasculature has for many years been considered as a passive system of distensible tubes designed to expose the entire cardiac output to alveolar gas in order to facilitate oxygen and carbon dioxide exchange. While this is a relatively simple concept, it requires an organ system of intricate design to provide the speed, efficiency of exchange, capacity and compactness[22] necessary for adequate and efficient function. The pulmonary circulation serves as a blood resevoir, a source of nutrition to the alveoli, a filter, a means of removing fluid from the alveoli and finally in pulmonary gas exchange.[22]

It is in this last capacity that it has received so much attention and investigation. For a variety of physical reasons there is variability in the regional distensibility and resistance to air flow,[46] and thus with inspiration some alveoli receive a greater proportion of the tidal volume than do others.

If indeed the vasculature served as a passive conduit for the cardiac output of the right side of the heart, it would be expected that poorly ventilated alvecli would be perfused along with adequately ventilated alveoli. The oxygen saturation of the pulmonary venous blood would surely vary with the slightest change in ventilation volume, rate, cardiac output and perfusion pressure. Yet it is known that pulmonary venous blood is almost fully saturated with oxygen and has a relatively constant carbon dioxide tension under a variety of conditions.[46] Thus it is apparent that a mechanism does exist whereby alveolar perfusion is regulated to match local alveolar ventilation and thus assures the precise control of gas exchange that occurs.

This mechanism has been the recipient of a tremendous amount of investigation and a source of great controversy. Some of the first recorded experiments designed to elucidate this mechanism studied the effects of asphyxiation upon systemic and pulmonary pressures.[46] In 1904 Plumier[92] found that a decrease in the oxygen tension of the inspired air elicited an increase in pulmonary pressure in the anesthetized dog. Von Euler and Liljestrand in 1946[43] studied the effects of changing the inspired gas composition upon the pulmonary arterial pressure (PAP) and theorized that changes in P_{O_2} and P_{CO_2} led to the local pulmonary vascular changes and thus redistributed the pulmonary blood flow from hypoventilated areas to well ventilated regions. Liljestrand[68] in 1958 proposed that the periods of hypoxia in cats led to an increased release of lactic acid locally, and it was this decrease in pH that was the chemical stimulus for vasoconstriction and consequent increase in PAP. This work stimulated Enson[42] to undertake a study to determine the effects of change in pH upon the PAP of patients with chronic respiratory disease. Enson describes a relationship between the hydrogen ion concentraion and the response to hypoxia. In these experiments severe hypoxia in the presence of a low (H+) was not associated with a pulmonary pressor response. However, the pulmonary vasculature was extremely sensitive to hypoxia if the (H+) was elevated.

Rudolph and Yuan in 1966[99] investigated the effects of varying degrees of hypoxia and (H+) upon the pulmonary vasculature of the newborn calf. They describe a relationship between pH level and response to hypoxia and correlated these changes with alterations in pulmonary vascular resistance.

These experiments and countless others have approached the subject of vasomotion and its control in the pulmonary vasculature from a variety of viewpoints. In general the experiments have been of three basic types. Observations have been made either in the pulmonary circulations of anesthetized mammals, in isolated lung preparations, or in patients with pulmonary disease. Each of these models is in some way artificial, and therefore fraught with potential errors.

The effects of anesthesia upon reflexes and vasomotor responses have been the subject of considerable debate, and the issue is far from resolved. Thilenius[108] demonstrated that the response of unanesthetized dogs to acute hypoxia could be altered by anesthesia and suggested that variability in results from various laboratories might be caused by different types and levels of anesthesia. Buckley[18] found that the modest increase of pulmonary vascular resistance in response to hypoxia was augmented by N_2O anesthesia and abolished by halothane. The use of isolated lung perfusion preparations similarly involves many sources of error. Fishman[46] points out that while such experiments allow for precise control of a large number of parameters, many artefacts are introduced due to the severing of nerve fibers, the use of non-physiological perfusates, and the deterioration of the heart and lungs.

Experiments involving cardiac catherization of patients are subject to criticism on several accounts. The anxiety patients experience anticipating cardiac catherization and the cooperation necessary during the procedure are frequently productive of artefacts. Perhaps more important, however, is the fact that indirect methods of obtaining data must be used. These usually include substitution of pulmonary artery wedge pressure for

left atrial pressures, and the use of the Fick method or dye dilution studies in the determination of cardiac output, rather than the generally more accurate measurements which can be obtained with an electromagnetic flow probe or the rotameter.

It is regrettable that the ideal experimental preparation has not yet been developed that will allow for precision of control and measurement without disturbing the normal physiology of the pulmonary vasculature. The previously reported studies often are lacking in various important facets of experimental design. New techniques may obviate some of these problems and provide a preparation which approaches more closely the ideal. It is hoped that the methods and procedures used in this investigation are a step in that direction.

The goals in initiating the present investigation were several: 1) to perform a qualitative and quantitative study of the effects of hypoxemia and acidemia as individual stimuli upon pulmonary arterial pressure, pulmonary vascular resistance, perfusion pressure, and left atrial pressure; 2) to determine the effects of acidemia and hypoxemia as combined stimuli upon the pulmonary vasculature; 3) to determine the effects of sympathetic stimulation upon the pulmonary vasculature. The experimental preparation and procedure were designed to provide a means of obtaining pulmonary pressure flow curves under a variety of conditions, and to provide a means of controlling and continually monitoring the following parameters:

1) Temperature

2) Systemic arterial pressure

3) Systemic arterial P_{O_2}

4) Systemic arterial pH

5) Cardiac output

6) Respiration

In addition the following parameters were continually measured:

1) Pulmonary arterial pressure (pulsatile and mean)

2) Left atrial pressure (pulsatile and mean)

3) Heart rate

Hematocrit was routinely measured periodically during the course of the procedures.

While this preparation was designed to be carried out in anesthetized adult cats, and suffers the possible disadvantage of anesthesia, its advantages are numerous. Of great importance is that the study was conducted with an intact pulmonary vasculature. Secondly, by means of a direct approach exposing the heart, lungs, and great vessels it was possible to obtain precise and direct measurements of pulmonary arterial and left atrial pressures simultaneously with cardiac output. Also systemic arterial pressure and cardiac output could be regulated as desired, allowing for reproducible pulmonary pressure-flow curves. Finally, the use of the Jewett flow-through electrode assembly allowed continuous recordings of arterial pH and P_{O_2}. This provided a new degree of reliable monitoring and control of oxygen tension and (H+) throughout the course of an entire experiment, and over the range of hypoxemia and acidemia studied.

II. PREPARATION

The experimental preparation was designed so that pressure-flow curves of the pulmonary circulation could be obtained. This entailed an open-chest preparation with monitoring of pulmonary artery, left atrial and systemic pressures, as well as cardiac output. By means of increasing or decreasing venous return to the right side of the heart, cardiac output could be varied and thus, pressures at various flow rates were ascertained. It was then possible to calculate pulmonary vascular resistance and plot pressure-flow curves. The preparation used to study the effects of sympathetic stimulation on the pulmonary vasculature was similar in design, however, it included separate perfusion of the animal's central nervous system.

The experimental animal chosen for these investigations was the adult mongrel cat. Animals were chose randomly without bias toward age, sex, breed or docility. Each experimental animal served as its own control, thus eliminating bias in selecting the group of experimental and control animals. Important in the selection procedure was the animal's weight and the presence of obvious respiratory disease. Cats were selected that had a minimum weight of at least five pounds (2.27 kgs) and maximum weight of nine poinds because of the rough correlation of the animal's size (weight) and size of the great vessels which were to be cannulated. Animals with grossly apparent respiratory illness were rejected, as were animals discovered to have pulmonary disease after thoracotomy. For each experimental animal, at least two and usually three animals were used as donors in order to obtain blood for the extracorporeal circuit, to be described in detail subsequently. These animals were also selected randomly.

Donor animals were anesthetized with an intraperitoneal (IP) injection of pentobarbital (25 mg/kg) or thiopental (25 mg/kg). Cannulation of a femoral artery was quickly performed, and the animals were then heparinized (10 mg/kg). A variable amount of 5% dextrose in 0.9% saline was then infused slowly and the animal was allowed to stabilize briefly, after which it was allowed to hemorrhage into a clean beaker. The hematocrit of this blood was determined, and blood with a hematocrit of less than 25% was not used in the experiment. The donor blood was then kept at 37°C in a water bath until used.

Cats for the experimental preparation were anesthetized with IP Diabutal (pentobarbital) in studies of acidosis and hypoxia, and with IP thiopental (25 mg/kg) supplemented with intravenous alpha-glucochloralase (15-25 mg/kg) in the studies of sympathetic stimulation.

With the cat in a supine position the femoral arteries and veins were exposed, ligated distally and cannulated with polyethylene tubing which had been primed with heparinized saline. With the neck fully extended a midline incision was made from the thyroid cartilage to the suprasternal notch. The trachea was exposed and incised between the cartilaginous rings. A large bore "T" shaped tracheostomy tube was inserted and doubly tied into place. One limb of the tube was connected to a valve and the other was left patent for spontaneous respirations.

The skin was incised in the midline the full length of the sternum and continued to the left along the costal margin to the angle of the ribs. The skin and subcutaneous tissue were bluntly dissected from the thoracic musculature and hemostasis was achieved with light ligatures. A midline incision of the muscles extending the length of the sternum was then made

and the thoracic cavity was entered. The animal's tracheostomy tube was immediately connected to a Harvard respirator and positive pressure ventilation continued for the duration of the experiment. Stroke volume was set to achieve expansion of the lungs to the limits of the thorax, and respiratory rate was arbitrarily set to maintain arterial P_{CO_2} at values less than 30 mm Hg. The sternum was then split from the xiphoid through the manubrium. The internal mammary arteries were isolated, doubly ligated and bisected. The left ribs (1-10) were doubly ligated and resected close to the vertebral column. The left pulmonary ligament was incised and the left lung was wrapped in a warm saline-soaked gauze and retracted to the right side. The descending thoracic aorta was fully visualized and the pleura covering it was incised longitudinally. The intercostal arteries (2-10) were ligated with 3-0 silk, and the left lung was allowed to re-expand.

A. ACIDEMIA

In the study using acidemia as a stimulus, the procedure continued as follows: The pericardium was incised and pushed posteriorly. With minimum dissection the main pulmonary artery was separated from the aorta and the electromagnetic flow probe was placed about the root of the aorta, taking care to avoid compression of the coronary arteries. The animal was then given heparin (10 mg/kg). The descending thoracic aorta was clamped proximally and distally, incised and doubly cannulated with the extracorporeal circuit (Fig. 1). Systemic arterial pressure could then be regulated within 1 mm Hg by means of a controlable constant pressure resevoir in the extracorporeal circuit. A small tributary of the

superior vena cava was cannulated with the venous return line from the aortic loop. A Sarns occlusive variable speed pump was used to systematically increase the venous return to the heart, and thus regulate cardiac output. The left atrium was subsequently cannulated with a flanged polyethylene cannula and connected to a Sanborn transducer. A purse string suture was placed in the right ventricular myocardium, which was then incised and a small gauge (P.E. 190) cannula was threaded through the outflow tract into the proximal portion of the main pulmonary artery. Pulmonary artery, left atrial and aortic pressures could then be measured with Sanborn transducers and recorded with a Sanborn 350 Direct Write Out Recorder. Heart rate was monitored with a Sanborn Cario-Tach by counting the pulmonary pulse wave frequency. Cardiac output, minus coronary flow was measured with the electro-magnetic flow probe and continuously recorded on the Sanborn direct writer. An arterial line from the aortic loop was connected to a Jewett flow-through electrode assembly which provided continuous measurements of pH and P_{O_2}.

B. HYPOXEMIA

The initial experiments investigating the effects of hypoxemia were performed with the same experimental preparation outlined above. The remainder of these experiments were performed with a slightly different preparation. After the intercostal arteries were ligated the left lung was allowed to re-expand. With minimal dissection the brachiocephalic and left subclavian arteries were isolated. There was no dissection about the root of the great vessels, and the electro-magnetic flow probe was not used. The animal was heparinized (10 mg/kg) and clamps were placed

on the thoracic aorta proximally and distally. The aorta was incised, double cannulated and the aortic clamps removed. Flow was then established through the extracorporeal aortic loop in the proximal limb of which was a Shipley-Wilson rotameter for continous measurement of cardiac output. The brachiocephalic and left subclavian arteries were then ligated, thus eliminating perfusion of the brain and diverting the entire cardiac output (minus coronary flow) into the aortic loop and through the rotameter. A venous return line and left atrial cannula were placed as described before.

A number 20 gauge needle with a polyethylene guard was then placed through the wall of the main pulmonary artery and connected to a Sanborn transducer thus providing accurate pulmonary arterial pressure traces. Again the Jewett flow-through assembly was connected to an arterial line from the extracorpeal loop, and the flow returned to a femoral vein.

C. SYMPATHETIC STIMULATION

The preparation designed to study the effects of sympathetic stimulation upon the pulmonary vasculature entailed producing intermittent CNS ischemia with a consequent autonomic discharge. The preparation was similar to those previously described with the exception that the braciocephalic artery was ligated proximally and cannulated distally with a line from the extracorporeal aortic loop. Great care was exercised to avoid air embolization at the time of cannulation. A Sigmamotor pump was used to perfuse the brachiocephalic vascular bed, including the CNS, at 100 mm Hg mean pressure. The left subclavian artery was again ligated leaving the

brachiocephalic artery as the predominant, if not exclusive, source of CNS perfusion. A venous return line was again connected from the aortic loop to a tributary of the superior vena cava. Left atrial, pulmonary pressures and cardiac output were measured as described in the hypoxemia preparation. Aortic and brachiocephalic pressures were measured by means of a large bore needle threaded through the wall of the polyethylene tubing of the proximal limb of the aortic loop and the branciocephalic perfusion line. The Jewett flow-through assembly was again connected to the aortic loop and femoral vein.(Fig. 2).

III. PROCEDURES

Immediately upon completion of the above preparation, the experimental procedure was begun. Sanborn transducers, calibrated against a mercury manometer, were placed at the level of the animal's right atrium and used at an attenuation most appropriate for the pressure to be measured. The sensitivity of each channel of the recorder was then adjusted using a standardized internal calibration signal corresponding to a predetermined number of millimeters of mercury. Rectal temperature was monitored by means of a thermistor, calibrated with a mercury thermometer, and was regulated by means of both local heat applied by means of a heating blanket beneath the animal, and by means of heat exchangers surrounding the tubing of the extracorporeal circuit. Respirations, which were initially spontaneous, were regulated by means of a Harvard positive pressure respirator after the thoracotomy had been initiated. Electromagnetic flow probes and the Shipley-Wilson rotameter had been calibrated and were balanced immediately prior to initiating the experiment. The

animal was then allowed to stabilize and the aortic pressure was regulated to a mean of 100 mm Hg. Prior to beginning the data collection, blood gases, hematocrit and temperature were determined and adjusted.

A. ACIDEMIA AND HYPOXEMIA

The data needed for the pressure flow curves were collected in the following manner. Each flow point on the pressure flow curve was evaluated for the pulmonary and left atrial pressures under control conditions, i.e., pH 7.35 to 7.45 and P_{O_2} more than 100 mm Hg. By increasing the venous return to the right side of the heart in increments, the pulmonary flow was increased in a closely controlled fashion. High speed pressure and flow tracings were recorded with each flow increment, and both mean and pulsatile values were compiled. Following the completion of the pressure-flow curve, the cardiac output was returned to the control level and arterial gases were again measured. Acidemia, hypoxemia or both were initiated in a controlled manner with constant monitoring of pH, P_{O_2} and P_{CO_2}.

Metabolic acidemia was produced by infusing 1 N lactic acid with a Harvard constant infusion pump until the desired pH was obtained. The acidemia could subsequently be corrected by similar infusions of sodium bicarbonate (44.6 mEq/cc). Arterial P_{O_2} was regulated by stepwise admixture of 95% O_2 or 100% N_2 to the inspired room air. Fine control of such admixtures permitted maintenance of arterial P_{O_2} at any desired level for prolonged periods of time. With the experimental conditions established and stable, another pressure-flow curve was obtained as was previously described. The experimental conditions that had prevailed throughout the

course of the pressure-flow measurements were then reversed, and upon re-establishment of stable control conditions, a third pressure-flow curve was obtained.

Of importance is the fact that subsequent to each adjustment of cardiac output, the flow was allowed to stabilize and the lungs were allowed to passively deflate for approximately one cycle prior to, and during the period in which each point of the pressure-flow curve was obtained. The presence of gross pulmonary edema, atelectasis, or irreversibility of the pressure-flow curve to the previous control level heralded the termination of the experiment. Any data which had been obtained under such conditions were considered invalid.

B. SYMPATHETIC STIMULATION

The procedure used for the study of the effects of sympathetic stimulation was carried out somewhat differently than that outlined above. In these studies after the establishment and control of basal conditions were achieved the preparation was assessed to determine whether or not it was reflexic. CNS ischemia was induced by shunting the blood from the brachiocephalic perfusion line to the venous return line without changing cardiac output or systemic pressure. The resultant autonomic discharge caused initial bradycardia, followed by a tachycardia. An increase in peripheral vascular resistance was indicated by a decrease in systemic flow and an increase in pressure as well as an increase in systemic pulse pressure. Tracings were obtained in all instances after a 90 second period of CNS ischemia, an interval which proved to provide a maximal stimulus as reflected in the above parameters. Animals that

were areflexic were eliminated from the study. Areflexia could be attributed to faulty technique in the great majority of cases. Reflexic animals were then given atropine, 1 mg IV, and parasympathetic block was considered established when a subsequent episode of transient CNS ischemia produced no bradycardia, but only a tachycardia.

The data collection was carried out in the following manner. For each level of flow three tracings were obtained: 1) a control tracing taken when CNS perfusion was intact and blood gases were stable at control levels; 2) following 90 seconds of CNS ischemia; 3) after CNS perfusion was re-established and cardiac rate and systemic pulse contour had returned to baseline conditions. Cardiac output was then increased and the sequence repeated. In this manner, three pressure-flow curves were obtained together. As in the experiments designed to study hypoxemia and/or acidemia, pH, P_{O_2}, temperature and aortic pressure were controlled at all times. In these experiments, also, after each adjustment of cardiac output, flow was allowed to stablize and the lungs allowed to passively deflate for approximately one cycle prior to and during the recording of each point of the pressure-flow curve. If in the control interval following the transient episode of ischemia, the conditions induced by ischemia were irreversible, or if pulmonary edema, atelectasis, or areflexia had occurred, the experiment was terminated and the data obtained were considered invalid. The observed hemodynamic changes were attributed to the sympathtic nervous system if upon completion of pressure-flow studies the infusion of TEAC (100 mg) blocked the tachycardia, peripheral resistance and pulse pressure changes that were previously noted during CNS ischemia.

Upon completion of data collection, all experimental animals were sacrificed prior to regaining consciousness. The position and patency of all cannulas was then ascertained and the pressure transducers were re-calibrated.

Throughout the course of all experiments arterial pH and P_{O_2} were continually monitored by means of a Jewett flow through device which contained Beckman pH and P_{O_2} electrodes. Values obtained with this assembly were frequently checked with simultaneous arterial samples used for measurements of pH, P_{O_2}, and P_{CO_2}. Apparatus for these measurements were a Beckman Model 160 pH meter and the Instrumentation Laboratory Model 113 P_{O_2}, P_{CO_2} gas analysis system. pH standardization was achieved using certified precision buffer solutions with checks within 0.01 pH units. P_{O_2} and P_{CO_2} electrodes were calibrated against known gas mixtures analyzed by the micro-Scholander method with agreement on P_{O_2} of $\pm$ 1 mm Hg at room air concentration, and P_{CO_2} values of $\pm$ 1 mm Hg over a range of 10-66 mm Hg P_{CO_2}.

All measurements were recorded on a Sanborn 350 direct writing recorder. The data obtained from these measurements permitted the construction of pressure-flow curves relating cardiac output (CO) to pulmonary arterial (PA), left atrial (LA) and net perfusion pressures at a constant mean aortic pressure (AOP). Pulmonary vascular resistance (PVR) was calculated according to the formula: PA-LA/flow (L per min) = Resistance Units. Data obtained according to the above manner were then compiled for analysis.

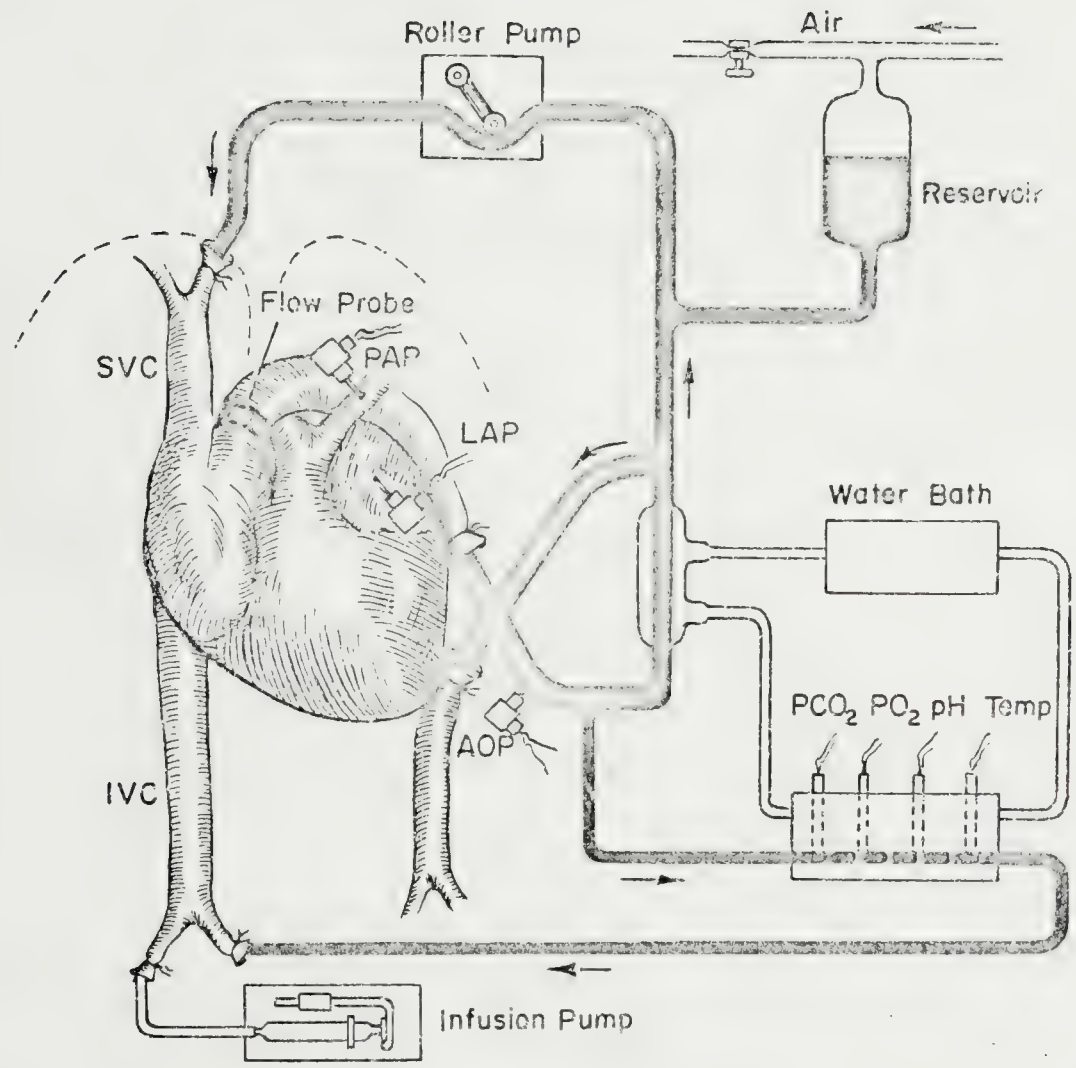

Fig. 1 Schematic drawing of cat heart-lung preparation designed for measurements of pulmonary pressure-flow curves.

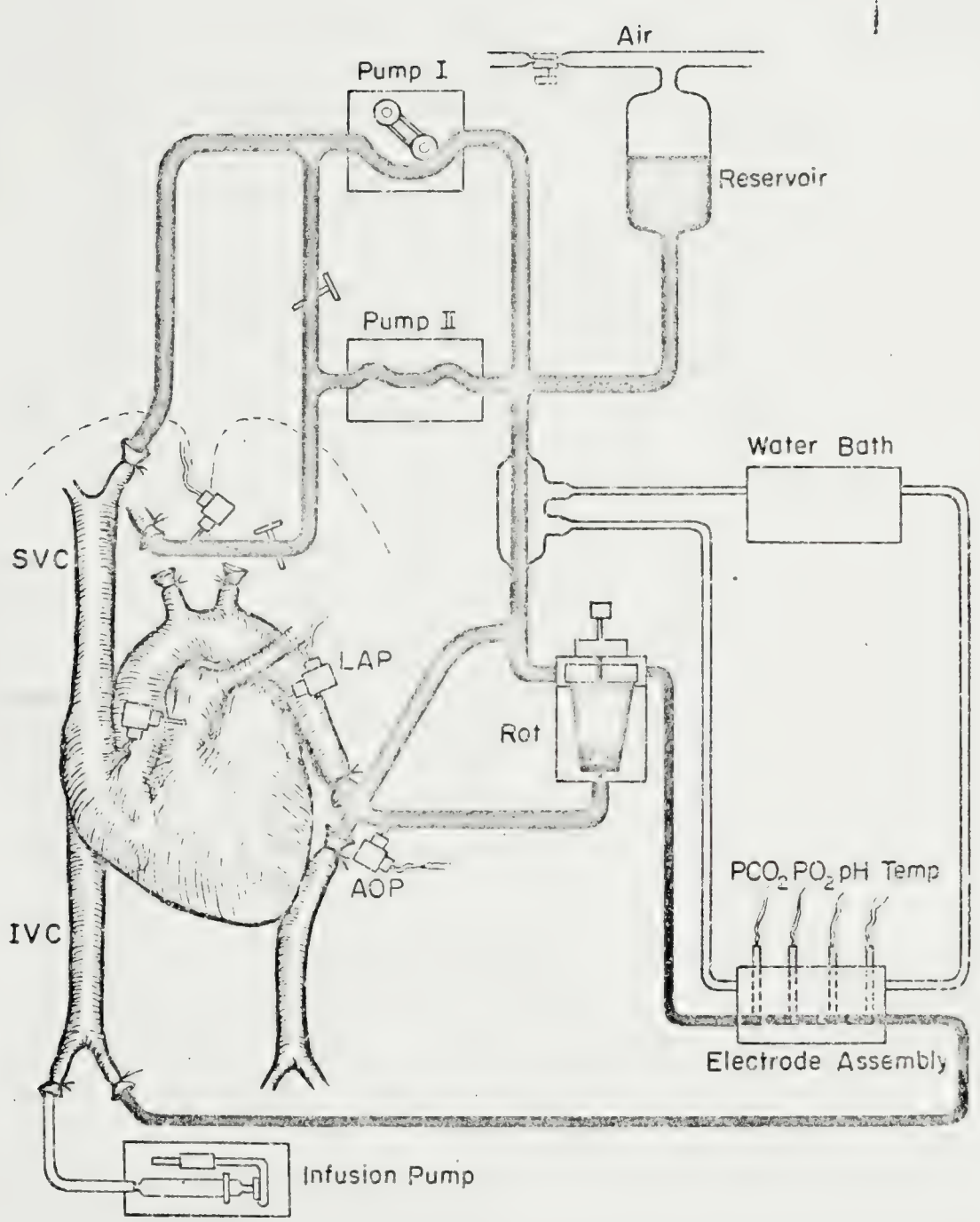

Fig. 2 Schematic drawing of cat heart-lung preparation with separate perfusion of the central nervous system.

IV. RESULTS

A. ACIDEMIA

Data are presented from a series of eight technically successful preparations in a total of eleven. An additional 22 cats were used as donor animals to provide priming blood for the extracorporeal circuit.

1. EFFECTS OF METABOLIC ACIDEMIA ON MEAN PULMONARY ARTERY PRESSURE

The reduction of arterial pH from a control at pH 7.40 by infusion of 1N lactic acid was associated with a shift of the pressure-flow curve toward the pressure axis in all preparations. Throughout the range of cardiac outputs achieved, the pulmonary pressure for a particular flow was increased during acidemia as compared to the control values at pH 7.40. For a greater degree of acidemia the magnitude of the change in the pressure-flow curve was found to increase. Similarly, upon correction of the acidemia by infusion of sodium bicarbonate until a pH of 7.40 was achieved, the mean pulmonary arterial pressure was found to return to the original control value for a particular flow. A representative example of such a change in pressure-flow curves is shown in Figure 3. The reversibility of these changes was clearly demonstrated by the return of the control curve to its original position. The arterial oxygen tension recorded during the course of the above experimental procedure was greater than 100 mm Hg and the animal temperature was constant at 36.5° C. The mean aortic pressure was maintained constant at 100 mm Hg.

2. EFFECTS OF METABOLIC ACIDEMIA ON LEFT ATRIAL PRESSURE

Left atrial pressure-flow curves were practically identical whether the animal was at control or acidemic pH values. Figure 4 shows the

left atrial pressure-flow curves for the experiment referred to in Figure 3, and demonstrates the relationship of the curves during both control and acid conditions. Upon examining the data from the entire group it was found that the LAP for a particular flow remained unchanged or decreased slightly from control during acidemia, but the magnitude of such changes was small. In most instances the mean LAP for a particular flow remained within 1 mm Hg of the value obtained during the previous control curve.

3. EFFECTS OF ACIDEMIA ON PERFUSION PRESSURE (PA-LA)

Since the LA pressure-flow curve was found to remain quite stable during the course of control and acidemic conditions, the relationship of perfusion pressure (PA-LA) to flow is of course similar to that of PAP to flow. Throughout the range of cardiac outputs achieved, the perfusion (PA-LA) for a given flow (C.O.) was increased during acidemia when compared to control values obtained at pH 7.35-7.45. Again upon correction of the acidemia, perfusion pressures returned to the previous control value. Figure 4 depicts changes in the perfusion pressure-flow curves for the same experiment. An increase in perfusion pressure for a given flow during acidemia was uniformly found in all experiments.

4. EFFECTS OF ACIDEMIA ON PULMONARY VASCULAR RESISTANCE (PVR)

Pulmonary vascular resistance was calculated according to the formula $\frac{\text{PA-LA}}{\text{flow}} \times 1000 = \text{Resistance Units}$. Resistance units were then in terms of mm Hg/L/min. As shown in Figure 4, when flow (C.O.) on the ordinate is plotted against resistance (PVR), a shift of the curve to the resistance axis was found during acidemia compared to control values. Hence, there was an increased vascular resistance for a given flow during acidemia. More severe degrees of acidemia resulted in greater shifts of the curve

to the right (Fig. 5). If pulmonary perfusion pressure (PA-LA) was plotted against resistance, the curve again was found to shift to the resistance axis during acidemia. An increased vascular resistance for a given perfusion pressure was observed during periods of acidemia, and therefore the amount of blood flow that could perfuse the lungs at a given perfusion pressure was decreased druing acidemia.

The original traces from a typical experiment of this series are shown in Figure 6. The tracings in the control panel were obtained at pH 7.46. The pH was then reduced by a slow infusion of 1N lactic acid. The tracings in the middle panel were obtained at pH 7.11, and those in the right panel were obtained at pH 6.96. With mean aortic pressure held constant and at the same cardiac output, the mean PAP was increased as a consequence of acidemia. The greater the magnitude of the acidemia the greater was the increase in mean PAP. The mean left atrial pressure was unchanged by the acidemia.

5. STATISTICAL ANALYSIS--ACIDEMIA

When comparing pressure-flow curves obtained from different animals it is imperative to select a means of standardization, in a sense a common denominator. In the analysis of the data which follows, pressures were taken from the pressure-flow curves at a flow rate selected according to the body weight of the animal in kilograms. The cardiac output per kilogram ratio was selected as that ratio which, when applied to all pressure flow curves, was within range of flow of the majority of the curves and which would therefore require the least number of extrapolations. Accordingly, a flow of 125 ml/kg was selected as the cardiac output at which pressures would be compared on the pressure-flow curves.

In Table 1 all data from the acidemia experiments have been compiled. Of note, the mean PA pressure during acidemia (pH 6.86-7.25) was 25.3 mm Hg with a standard error of 1.07, as compared with the mean PA pressure during control periods (pH 7.35-7.45) of 19.5 mm Hg with a standard error of 0.61. In the column ΔPA of Table 1, the (PA acidemia) minus (PA control) was determined for each experimental curve and the mean change in PA (ΔPA) pressure was calculated to be 5.8 mm Hg with a standard error of 0.74. When the data for mean PA pressure during acidemia and control periods was subjected to a "t" test the value $p<.001$ was obtained, and the two groups therefore were considered significantly apart.

The mean LA pressure during acidemia was 6.4 mm Hg with a standard error of 0.53 as compared to the mean LA pressure during control periods of 6.3 mm Hg with a standard error of 0.46. The two groups were not significantly different ($.9>p<.8$).

The results obtained for perfusion pressure (PA-LA) paralleled that of PA pressures. The mean PA-LA during acidemia was 18.9 mm Hg with a standard error of 1.17, as compared with a mean PA-LA during control periods of 13.1 with a standard error of 0.78. In the column ΔPA-LA of Table 1, the (PA-LA acidemia) minus (PA-LA control) was determined for each experimental curve and the mean ΔPA-LA was calculated to be 5.7 mm Hg with a standard error of 0.76. The data comparing PA-LA during acidemia with control periods were significantly different ($p < .001$). These findings are depicted in Figure 7.

The range of acidosis in the eight experiments under discussion was from pH 6.86 to pH 7.25. As was previously mentioned, it was repeatedly found that an increasing degree of acidemia produced a greater magnitude

of response in the pulmonary vasculature as reflected by the pressure-flow curves. Therefore, the data obtained was arbitrarily subdivided into two groups as follows: 1) pH 7.16-7.25 and 2) pH 6.86-7.15. Statistical analysis of these data was then carried out, comparing each of these two groups with control, and then comparing the groups with each other. These data are presented in Table 2.

MODERATE ACIDEMIA (pH 7.16-7.25)

In five animals a total of six pressure-flow curves were obtained during conditions of moderate acidemia. Of note, the mean PA pressure during acidemia was 24.7 mm Hg with a standard error of 1.37, as compared to the mean pressure during control periods of 19.5 mm Hg with a standard error of 0.61. The calculated mean ΔPA was 3.9 mm Hg with a standard error of 0.96. These two groups were considered to be significantly apart ($p < .001$). The mean LA pressure during acidemia was 5.9 mm Hg with a standard error of 0.56 as compared to a control LA pressure of 6.3 mm Hg with a standard error of 0.46. These values were not considered to be significantly apart ($.7 > p < .5$). The pulmonary perfusion pressure (PA-LA) during acidemia was 18.8 mm Hg with a standard error of 1.79 compared to control PA-LA of 13.1 mm Hg (S.E. = .78). These values were considered to be significantly apart ($p < .001$).

SEVERE ACIDEMIA (pH 6.86-7.15)

In seven animals a total of twelve pressure-flow curves were obtained during periods of severe acidemia. The mean PA pressure was 25.6 mm Hg with a standard error of 1.48 as compared to the mean PAP control of 19.5 mm Hg with a standard error of 0.61. The mean $_{\Delta}$PA was calculated to be 6.7 mm Hg with a standard error 0.91. The values for PAP acidemia

were considered significantly apart from PAP control ($p<.001$). The mean LA pressure during acidemia was 6.7 mm Hg with a standard error of 0.75 as compared to the LAP control of 6.3 mm Hg with a standard error of 0.46. PA-LA pressure during acidemia was 18.9 mm Hg. with a standard error of 1.56 as compared to PA-LA control of 13.1 mm Hg with a standard error of 0.78. The mean ΔPA-LA was calculated to be 6.4 mm Hg with a standard error of 1.02. The PA-LA acidemia was considered to be significantly apart from PA-LA control ($p<.001$).

COMPARISON OF MODERATE AND SEVERE ACIDEMIA

The mean PAP during severe acidemia was 25.6 mm Hg compared to the PAP during moderate acidemia of 24.7 mm Hg. These two values were not considered significantly different ($.9>p<.7$). The average PA-LA with severe acidosis was 18.9 mm Hg compared to the PA-LA during moderate acidemia of 18.8 mm Hg. Again these values are not significantly different.

Figure 7 depicts the mean PA and PA-LA pressures along with their standard errors from the data on acidemia.

Table 1

DATA AND STATISTICAL ANALYSIS

Values from Pressure Flow Curves at 125 ml/kg Flow

		pH 7.35 - 7.45			pH = 6.86 7.25				
ANIMAL	C.O.	Mean PA	LA	PA-LA	PA	LA	PA-LA	ΔPA	ΔPA-LA
A-8	340	(16.7)	(1.0)	15.7	(19.7)	2.3	17.4	3.0	1.7
2.73 kg	340	(14.2)	(7.0)	7.2	20.0	6.0	14.0	5.8	6.8
	340	17.0	6.0	11.0	(22.0)	(5.4)	16.6	5.0	5.6
A-9	340	17.0	5.0	12.0	22.0	4.0	18.0	5.0	6.0
2.73 kg									
A-10	340	18.0	8.0	10.0	22.5	7.5	15.0	4.5	5.0
2.73 kg	340	18.0	8.0	10.0	26.0	7.0	19.0	8.0	9.0
	340	18.2	8.3	9.9	29.0	10.7	18.3	10.8	8.4
A-12	455	(21.2)	(4.0)	17.2	(27.5)	(4.4)	23.1	6.3	5.9
3.64 kg	455	(21.2)	(4.0)	17.2	(31.0	(7.7)	23.3	9.8	6.1
A-13	340	(21.8)	(8.0)	13.8	(22.4)	(7.0)	15.4	0.6	1.6
2.73 kg	340	(21.8)	(8.0)	13.8	(27.7)	(9.4)	18.3	5.9	4.5
A-16	364	20.3	7.7	12.6	27.6	8.4	19.2	7.3	6.6
2.91 kg	364	19.9	7.6	12.3	21.9	8.0	13.9	2.0	1.6
	364	19.9	7.6	12.3	22.7	8.8	13.9	2.8	1.6
A-17	340	24.0	5.0	19.0	(37.0)	3.0	34.0	13.0	15.0
2.73 kg	340	24.0	5.0	19.0	30.0	5.0	25.0	6.0	6.0
A-18	488	18.8	7.0	11.8	22.0	5.0	17.0	3.2	5.2
3.90 kg	488	18.8	7.0	11.8	24.2	5.7	18.5	5.4	6.7
Total		350.8	114.2	236.6	455.20	115.30	339.90	104.40	103.30
n		18	18	18	18	18	18	18	18
Mean		19.5	6.3	13.1	25.3	6.4	18.9	5.8	5.7
Standard Deviation		2.58	1.97	3.31	4.53	2.26	4.95	3.15	3.22
Standard Error		.61	.46	.78	1.07	.53	1.17	.74	.76
"T" Test					p<.001	p<.8	p<.001		

Table 2

DATA AND STATISTICAL ANALYSIS

Values from Pressure Flow Curves at 125 ml/kg Flow

		pH 7.35 - 7.45			pH 6.86 - 7.15					pH 7.16 - 7.25				
ANIMAL	C.O.	Mean PA	LA	PA-LA	PA	LA	PA-LA	Δ PA	Δ PA-LA	PA	LA	PA-LA	Δ PA	Δ PA-LA
A-8	340	(16.7)	(1.0)	15.7	(19.7)	2.3	17.4	3.0	1.7					
2.73 kg	340	(14.2)	(7.0)	7.2	20.0	6.0	14.0	5.8	6.8					
	340	17.0	6.0	11.0	(22.0)	(5.4)	16.6	5.0	5.6					
A-9	340	17.0	5.0	12.0	22.0	4.0	18.0	5.0	6.0					
2.73 kg														
A-10	340	18.0	8.0	10.0	22.5	7.5	15.0	4.5	5.0					
2.73 kg	340	18.0	8.0	10.0	26.0	7.0	19.0	8.0	9.0					
	340	18.2	8.3	9.9	29.0	10.7	18.3	10.8	8.4					
A-12	455	(21.2)	(4.0)	17.2						(27.5)	(4.4)	23.1	6.3	5.9
3.64 kg					(31.0)	(7.7)	23.3	9.8	6.1					
A-13	340	(21.8)	(8.0)	13.8						(22.4)	(7.0)	15.4	0.6	1.6
2.73 kg	340				(27.7)	(9.4)	18.3	5.9	4.5					
A-16	364	20.3	7.7	12.6	27.6	8.4	19.2	7.3	6.6					
2.91 kg	364	19.9	7.6	12.3						21.9	8.0	13.9	2.0	1.6
	364	19.9	7.6	12.3	22.7	8.8	13.9	2.8	1.6					
A-17	340	24.0	5.0	19.0	(37.0)	(3.0)	34.0	13.0	15.0					
2.73 kg	340	24.0	5.0	19.0						30.0	5.0	25.0	6.0	6.0
A-18	488	18.8	7.0	11.8						22.0	5.0	17.0	3.2	5.2
3.90 kg	488	18.8	7.0	11.8						24.2	5.7	18.5	5.4	6.7
Total		350.8	114.2	236.6	307.2	80.2	22.70	80.9	76.3	148.0	35.1	112.9	23.5	27.0
n		18	18	18	12	12	12	12	12	6	6	6	6	6
Mean		19.5	6.3	13.1	25.6	6.7	18.9	6.7	6.4	24.7	5.9	18.8	3.9	4.5
Standard Deviation		2.58	1.97	3.31	5.13	2.61	5.40	3.15	3.52	3.36	1.38	4.38	2.34	2.30
Standard Error		.61	.46	.78	1.48	.75	1.56	.91	1.02	1.37	.56	1.79	.96	.94
"T" Test					p<.001	p<.5	p<.001			p<.001	p<.5	p<.001		

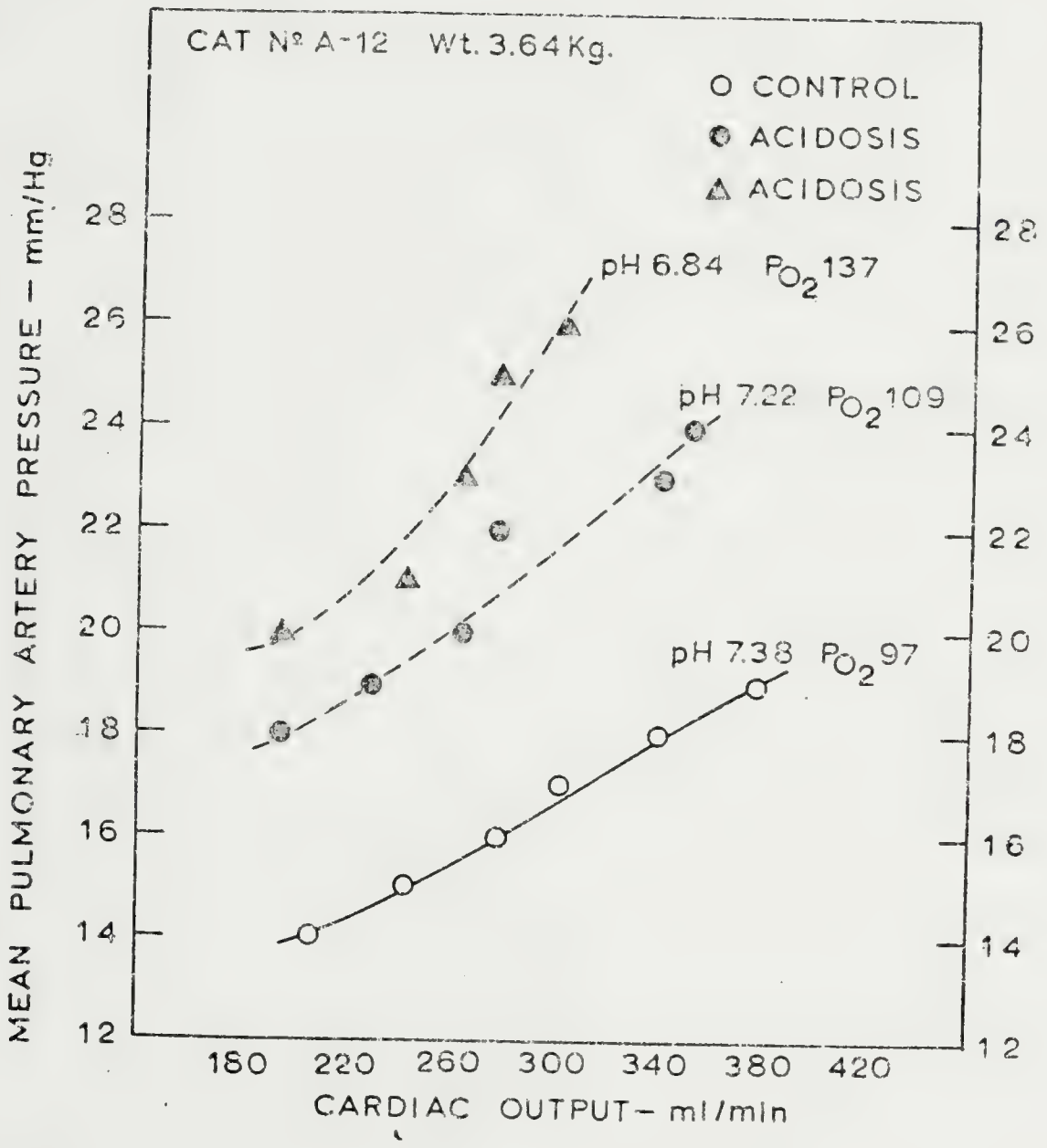

Fig. 3 Pressure-flow curves of the pulmonary vasculature showing a shift of the curve to the pressure axis with metabolic acidemia. With a greater degree of acidemia a more pronounced shift of the pressure-flow curve occurs.

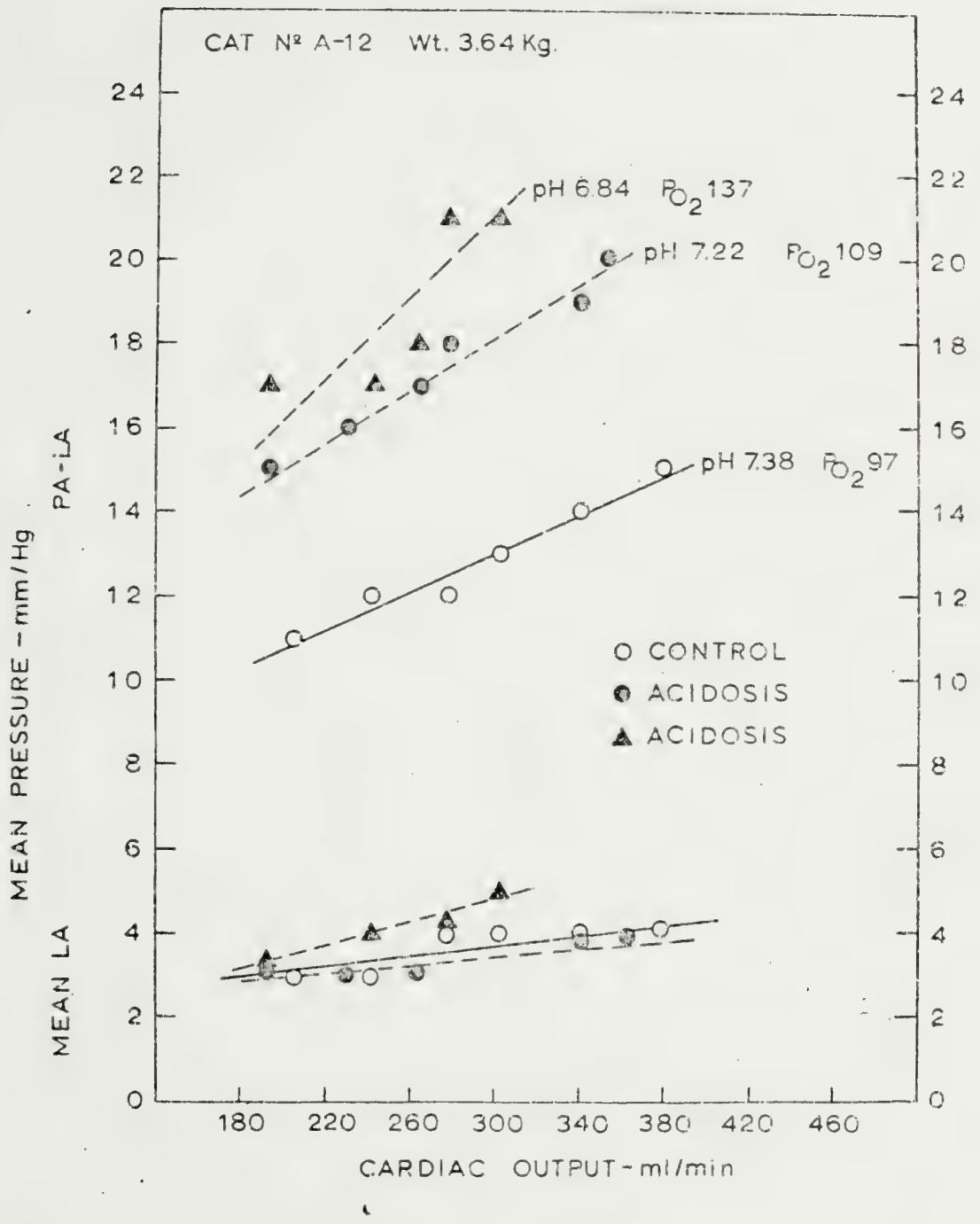

Fig. 4 Left atrial pressure-flow curves and perfusion (PA-LA) pressure-flow curves are depicted. Of note, the left atrial curves remain unchanged in the face of metabolic acidemia. Perfusion pressure-flow curves parallel the pulmonary artery pressure-flow curves and shift to the pressure axis in response to acidemia.

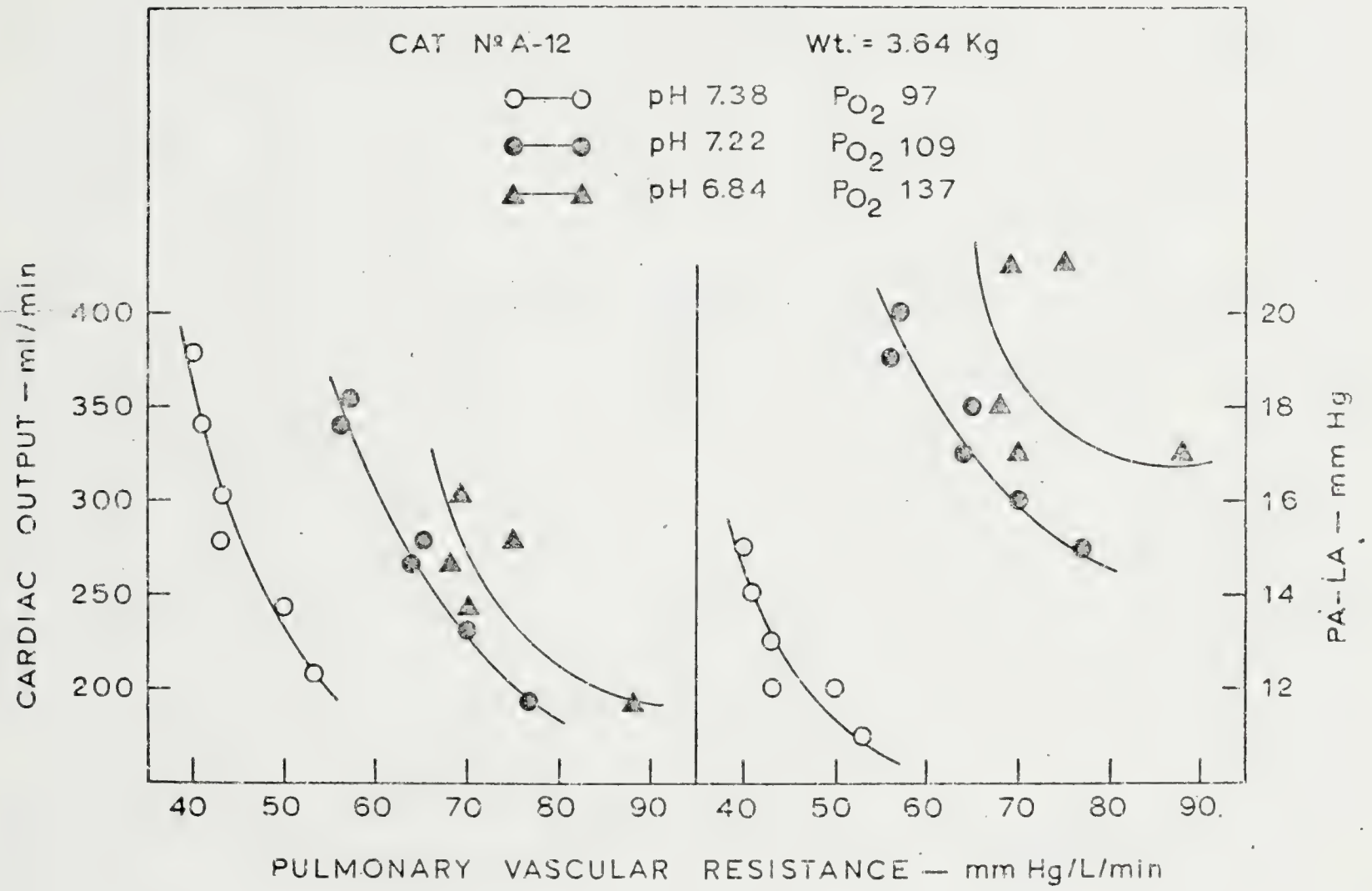

Fig. 5 Pulmonary vascular resistance is plotted against both cardiac output and perfusion pressure. Both curves are noted to shift toward the resistance axis in a graded fashion in response to acidemia.

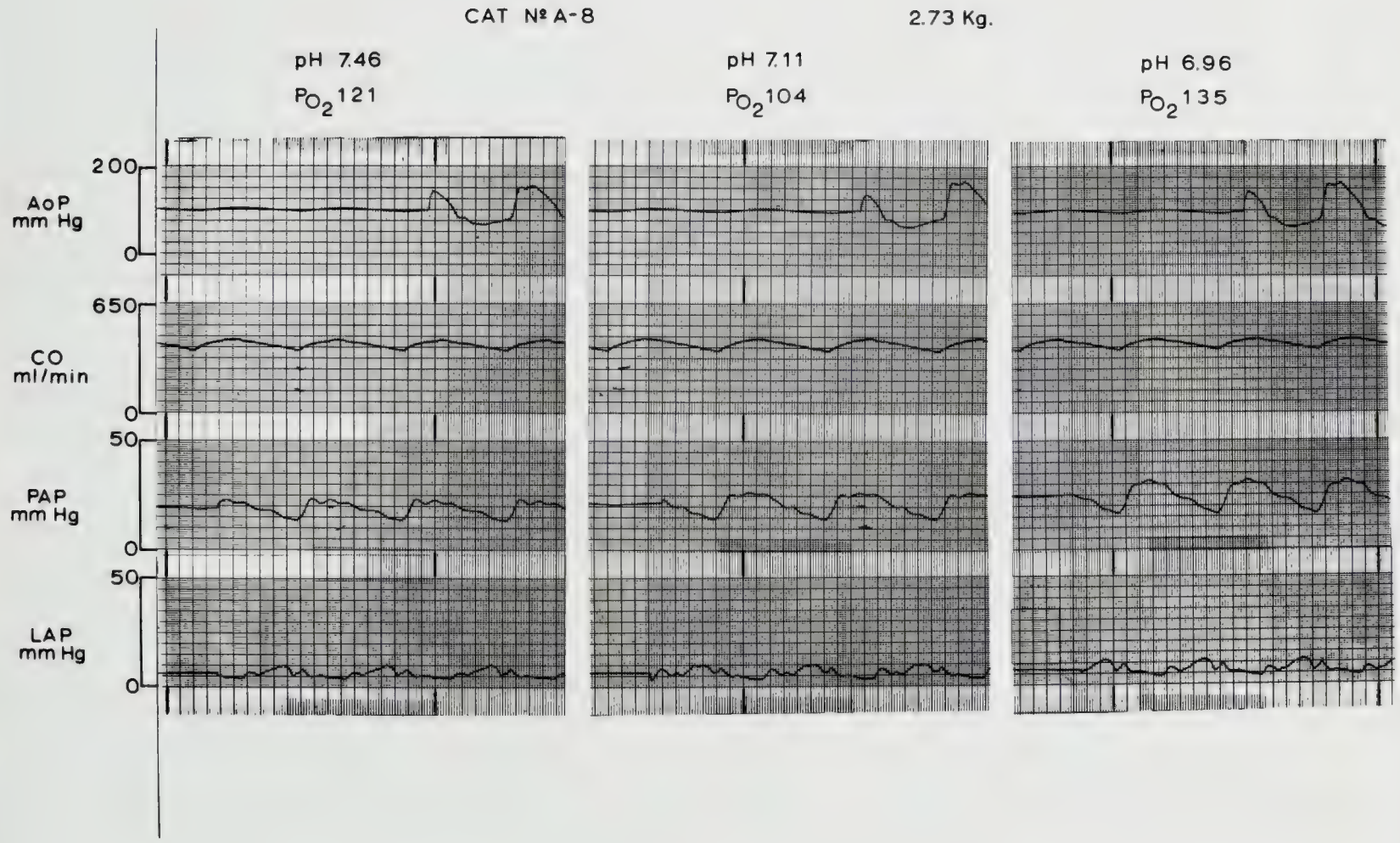

Fig. 6 Original traces obtained from a cat showing the relationship of PAP and LAP to flow (C.O.) in response to varying degrees of acidemia. Chart speed = 100 mm/sec. At a constant aortic pressure and cardiac output, PAP rises progressively with increasing severity of acidemia with no concomitant increase in LAP.

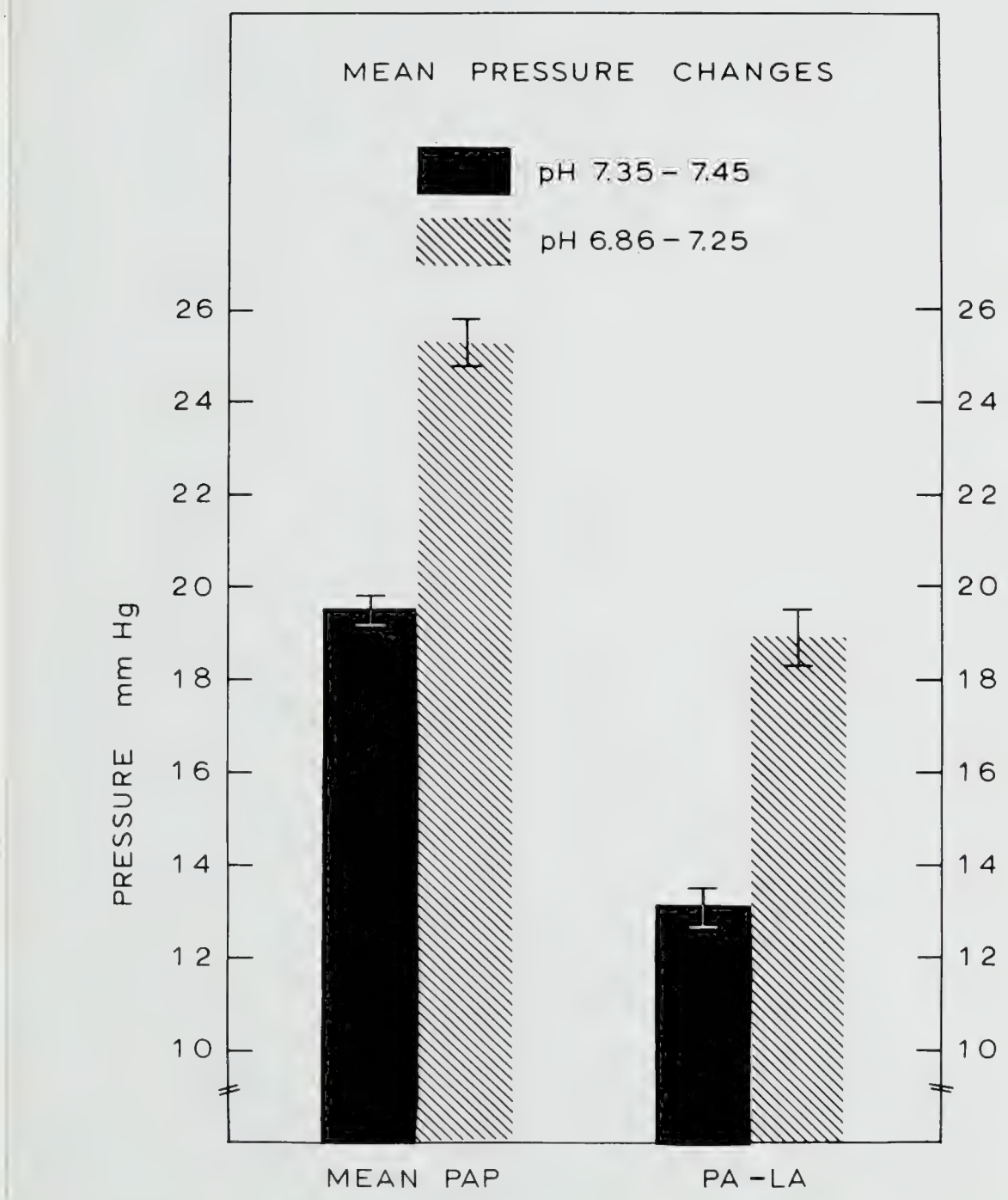

Fig. 7 Bar graph depicts the mean PA and PA-LA pressures along with their standard errors during both control and acidemic conditions.

B. HYPOXEMIA

Data are presented from a series of fourteen technically successful experiments in a total of eighteen. Additionally, 36 cats were used as donor animals to provide blood for the extracorporeal circuit.

1. EFFECTS OF HYPOXEMIA ON MEAN PULMONARY ARTERY PRESSURE (PAP)

Systemic arterial P_{O_2} was reduced from control levels of >100 mm Hg to a range of 25-58 mm Hg by means of a gas mixing device which allowed the addition of controlled amounts of N_2 or O_2 to the room air, thus regulating the O_2 content of the inspired air. With this device it was possible to maintain the animal's arterial P_{O_2} at any given level with great accuracy. The reduction of systemic arterial P_{O_2} from control levels of >100 mm Hg by changing the inspired air O_2 content was associated with a shift of the pressure-flow curve toward the pressure axis. Throughout the range of cardiac outputs achieved, the pulmonary pressure for a particular flow was found to be increased during hypoxemia as compared to control values. This response occurred in all animals tested. However, the response in some was far more striking than in others. Upon correction of the induced hypoxemia by increasing the O_2 content of the inspired air, mean pulmonary pressures were found to return to the original control values for a particular flow. A representative example of such a change in pressure-flow curves is shown in Figure 8.

In several experiments arterial P_{O_2} was brought to more than one hypoxemia level. For a greater degree of hypoxemia the magnitude of the change in the pressure-flow curve was found to increase. Thus, the mean PA pressure for a particular flow was higher than the mean PA pressure

during less severe hypoxemia. Figure 9 shows a representative series of pressure-flow curves in which two levels of hypoxemia were maintained. During the course of all such experiments mean aortic pressure was maintained constant at 100 mm Hg and animal temperature was maintained between 36.5° C and 37.5° C.

2. EFFECTS OF HYPOXEMIA ON LEFT ATRIAL PRESSURE (LAP)

Left atrial pressure-flow curves during hypoxemia were practically identical to those obtained during control period (P_{O_2} > 100 mm Hg). Left atrial pressure varied during hypoxemia, sometimes to lower than control values, occasionally to higher than control values. However, all such changes were small from -1.2 mm Hg to +1.6 mm Hg from control. Figure 10 shows left atrial pressure-flow cuves for the same experiment depicted in Figure 9. The LA pressure for a particular flow was essentially identical during hypoxemia and control periods.

3. EFFECTS OF HYPOXEMIA ON PERFUSION PRESSURE (PA-LA)

When perfusion pressure-flow curves were plotted, they closely resemble the pulmonary artery pressure-flow curves previously presented. Throughout the range of cardiac outputs achieved, the perfusion pressure (PA-LA) for a given flow (C.C.) was increased during hypoxemia as compared to control values obtained at P_{O_2} > 100 mm Hg. Again, upon correction of hypoxemia, perfusion pressure returned to the previous control values. Figure 10 depicts the changes in the perfusion pressure-flow curves for the same experiment depicted in Figure 9. An increase in the perfusion pressure for a given flow during hypoxemia was uniformly found in all experiments.

4. EFFECTS OF HYPOXEMIA ON PULMONARY VASCULAR RESISTANCE

Pulmonary vascular resistance was calculated as indicated above. When flow was plotted against resistance a shift of the curve toward the resistance axis was found during hypoxemia as compared to control. Thus, there was increased vascular resistance for a given flow during hypoxemia. Similarly if perfusion pressure (PA-LA) was plotted against resistance, this curve also shifted toward the resistance axis during hypoxemia as compared to control. Thus, there was an increased vascular resistance for a given perfusion pressure during the periods of hypoxemia, and the amount of blood flow that could perfuse the lungs at a given perfusion pressure was decreased.

The original traces from such an experiment are shown in Figure 11. The tracings in the control panel were obtained at pH 7.34 and P_{O_2} 148. The tracings shown in the middle panel were obtained at pH 7.40 and P_{O_2} 30. The mean aortic pressure was held constant at 100 mm Hg and the animal temperature was 37° C. At the same levels of cardiac output, the mean PAP is increased during hypoxemia. The mean LA pressure for the same cardiac output did not change, however.

5. STATISTICAL ANALYSIS--HYPOXEMIA

In an effort to standarize the data, pressures were taken from the pressure-flow curves at a flow rate of 150 ml/kg/min as described above.

In Tabel 3, all data from the hypoxemia experiments have been compiled. The mean PA pressure during hypoxemia was found to be 20.6 mm Hg (S.E. = 0.83), as compared to a mean PA pressure during control periods of 17.3 mm Hg (S.E. = 0.67). In the column ΔPA of Table 3, the PA hypoxemia minus PA control was calculated to be 3.4 mm Hg (S.E. = 0.43). When the data

for mean PA pressure during hypoxemia and control periods was subjected to a "t" test, the p value <.001 was obtained, confirming that the two groups are significantly different.

The mean LA pressure during hypoxemia was 5.2 mm Hg (S.E. = 0.36), as compared to a mean LA pressure during control periods of 5.0 mm Hg (S.E. = 0.35). These values were not significantly different (.7>p<.5). As would be expected the data obtained for perfusion (PA-LA) pressures paralleled that concerning PA pressures. The mean PA-LA during hypoxemia was 15.5 mm Hg (S.E. = 0.72). The mean PA-LA during control periods of 12.3 mm Hg (S.E. = 0.58). In the column ΔPA-LA of Table 3, the (PA-LA hypoxemia) minus (PA-LA control) was calculated for each curve and the mean ΔPA-LA was calculated to be 3.2 mm Hg (S.E. = 0.45). When the data was subjected to the "t" test the value p<.001 was obtained, confirming that the two groups are significantly apart. Figure 12 depicts the mean PA and PA-LA pressure changes with the standard errors from the data on hypoxemia.

While it remains true that a more severe level of hypoxemia was associated with an increased magnitude of response as seen in individual experiments, it was not possible to divide the data into groups representing different levels of hypoxemia. This may be a reflection of the fact that the level of hypoxemia in the majority of experiments was between P_{O_2} 30-45. Few experiments were conducted at more extreme levels of hypoxemia.

Table 3

DATA AND STATISTICAL ANALYSIS

Values from Pressure Flow Curves at 150 ml/kg Flow

	CONTROL				HYPOXEMIA			Δ	
ANIMAL	C.O.	Mean PA	LA	PA-LA	PA	LA	PA-LA	ΔPA	ΔPA-LA
C-1	462	(11.4)	5.4	6.0	15.6	6.5	9.1	4.2	3.1
	462	(11.4)	5.4	6.0	(21.1)	4.8	7.3	0.7	1.3
C-2	546	(18.9)	2.3	16.6	(20.6)	3.3	17.3	1.7	0.7
	546	18.2	2.8	15.4	20.4	3.5	16.9	2.2	1.5
	546	16.4	3.3	13.1	21.0	3.3	17.7	4.6	4.6
C-3	410	15.2	3.6	11.6	15.9	3.4	12.5	0.7	0.9
	410	15.4	5.3	10.1	17.3	4.6	12.7	1.9	2.6
	410	15.9	3.8	12.1	19.1	3.3	15.8	3.2	3.7
C-4	410	(22.4)	(4.6	17.8	25.5	4.5	21.0	3.1	3.2
C-5	410	15.9	3.0	12.9	17.1	4.0	13.1	1.2	0.2
	410	15.3	3.7	11.6	17.4	3.4	14.0	2.1	2.4
C-7	410	19.9	4.9	15.0	23.5	6.5	17.0	3.6	2.0
	410	19.8	4.8	15.0	(22.9)	5.9	17.0	3.1	2.0
C-8	435	12.0	212	9.8	17.0	3.2	13.8	5.0	4.0
	435	14.0	3.7	10.3	16.0	3.3	12.7	2.0	2.4
	435	13.2	4.9	8.3	16.4	3.7	12.7	3.2	4.4
C-9	435	16.7	6.5	10.2	18.1	6.5	11.6	1.4	1.4
	435	16.7	6.5	10.2	19.3	6.5	12.8	2.6	2.6
C-10	410	22.3	7.0	15.3	(27.9)	6.4	21.5	5.6	6.2
C-11	435	16.0	4.7	11.3	19.2	5.0	14.2	3.2	2.9
	435	16.4	4.9	11.5	(27.0)	4.3	22.7	10.6	11.2
C-12	410	23.2	6.0	17.2	27.0	5.7	21.3	3.8	4.1
DATA OF PREPARATION WITH PERFUSION CNS									
A-8	410	18.0	5.3	12.7	24.0	6.0	18.0	6.0	5.3
	410	18.0	7.0	11.0	25.9	7.0	18.9	7.9	7.9
A-9	410	18.0	5.3	12.7	19.9	5.0	14.9	1.9	2.2
A-16	435	(22.5)	9.0	13.5	(25.4)	(9.4)	16.0	2.9	2.5
	435	(23.4)	(9.7)	13.7	(25.6)	(10.4)	15.2	2.2	1.5
Total		466.5	135.6	330.9	447.1	139.4	417.7	90.2	86.8
n									
Mean		17.3	5.0	12.3	20.6	5.2	15.5	3.4	3.2
Standard Deviation		3.47	1.82	3.00	4.29	1.87	3.72	2.21	2.36
Standard Error		.67	.35	.58	.83	.36	.72	.43	.45
Data Range Low		11.4	2.2	6.0	12.1	3.2	7.3	.7	.2
High		23.4	9.7	17.8	27.9	10.4	22.7	10.6	11.2
"T" Test					p< .001	p< .5	p< .001		

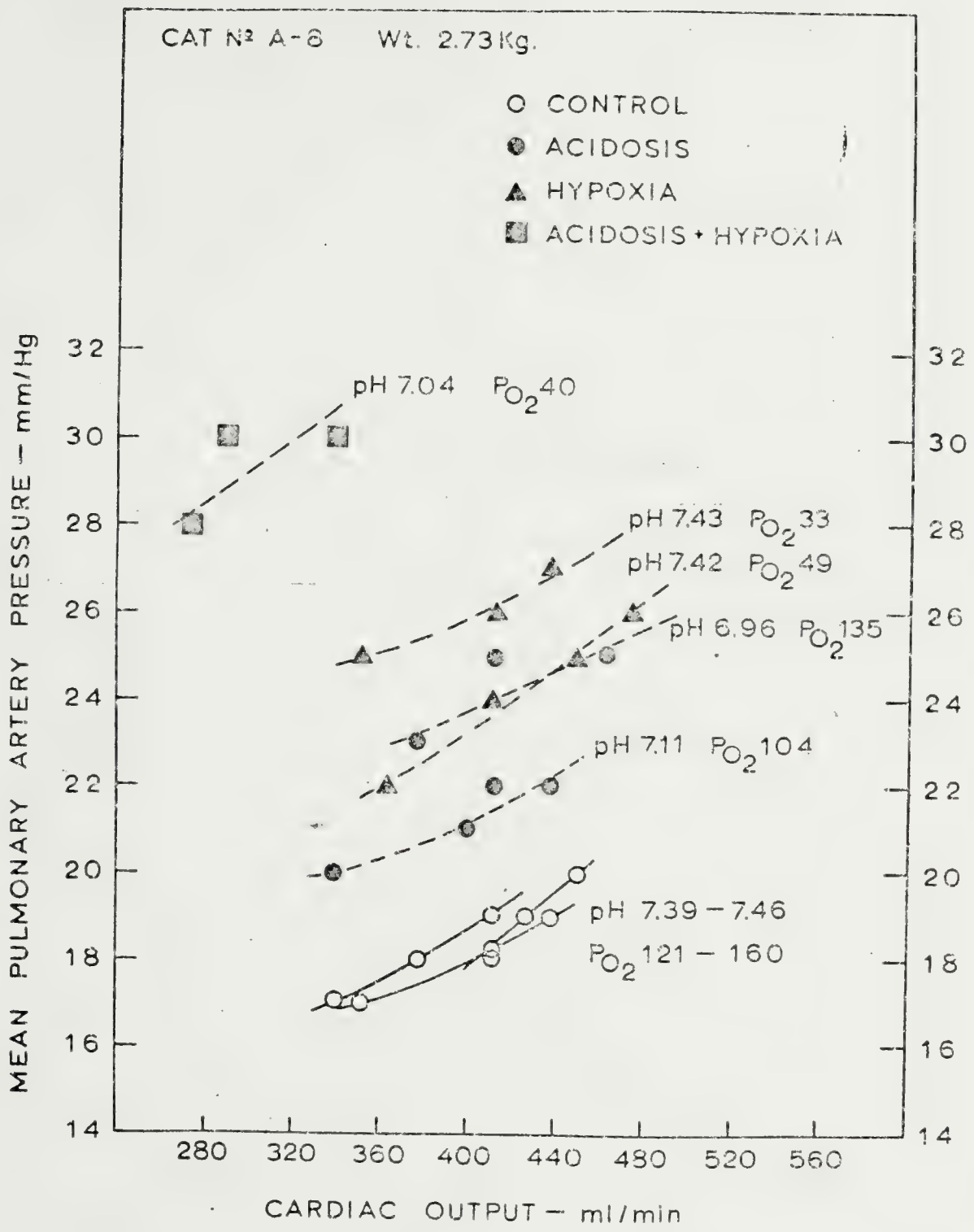

Fig. 8 Pulmonary artery pressure-flow curves showing a shift of the curve toward the pressure axis in response to hypoxemia, acidemia and a combination of both hypoxemia and acidemia. Reversibility of this effect is shown by the virtually superimposed control curves obtained throughout the experiment.

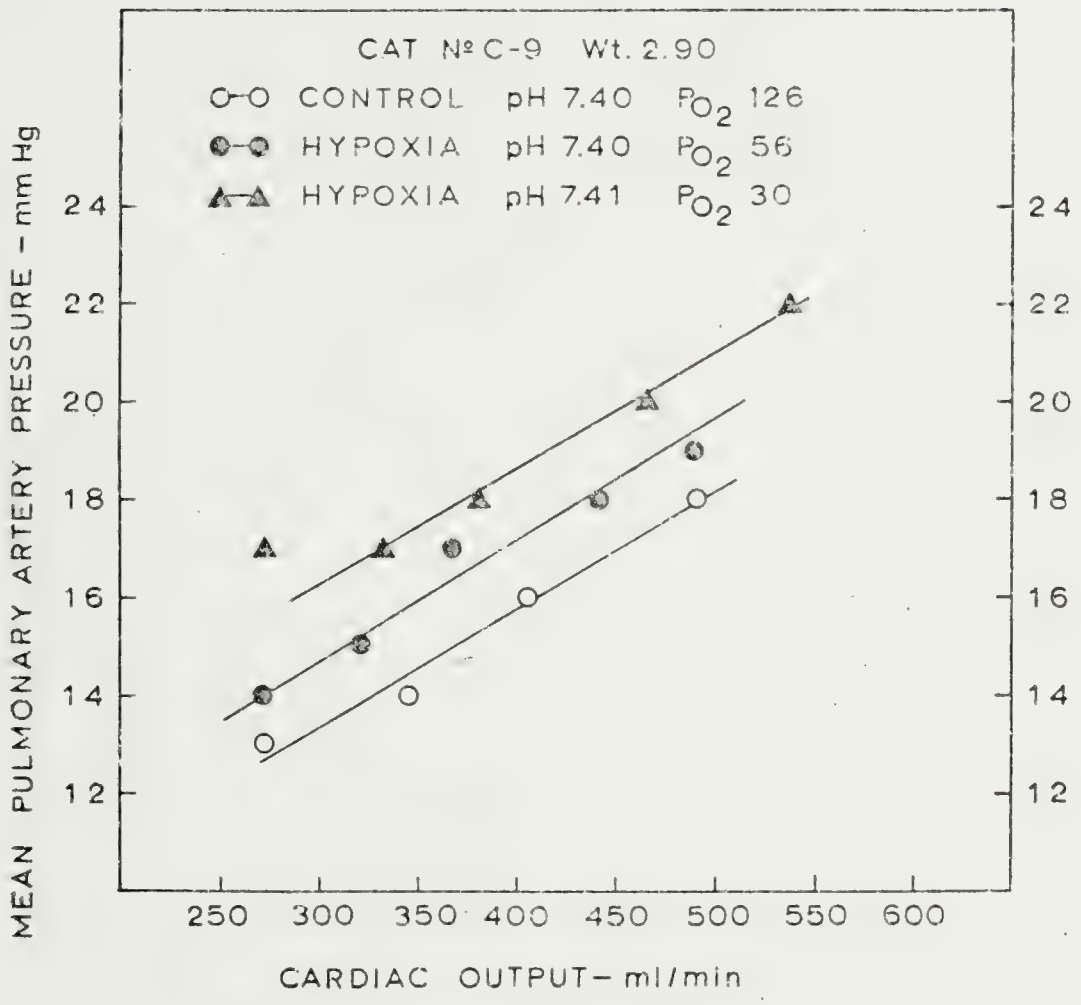

Fig. 9 Pulmonary artery pressure-flow curves depicting a graded shift of the curve toward the pressure axis in response to increasing severity of hypoxemia.

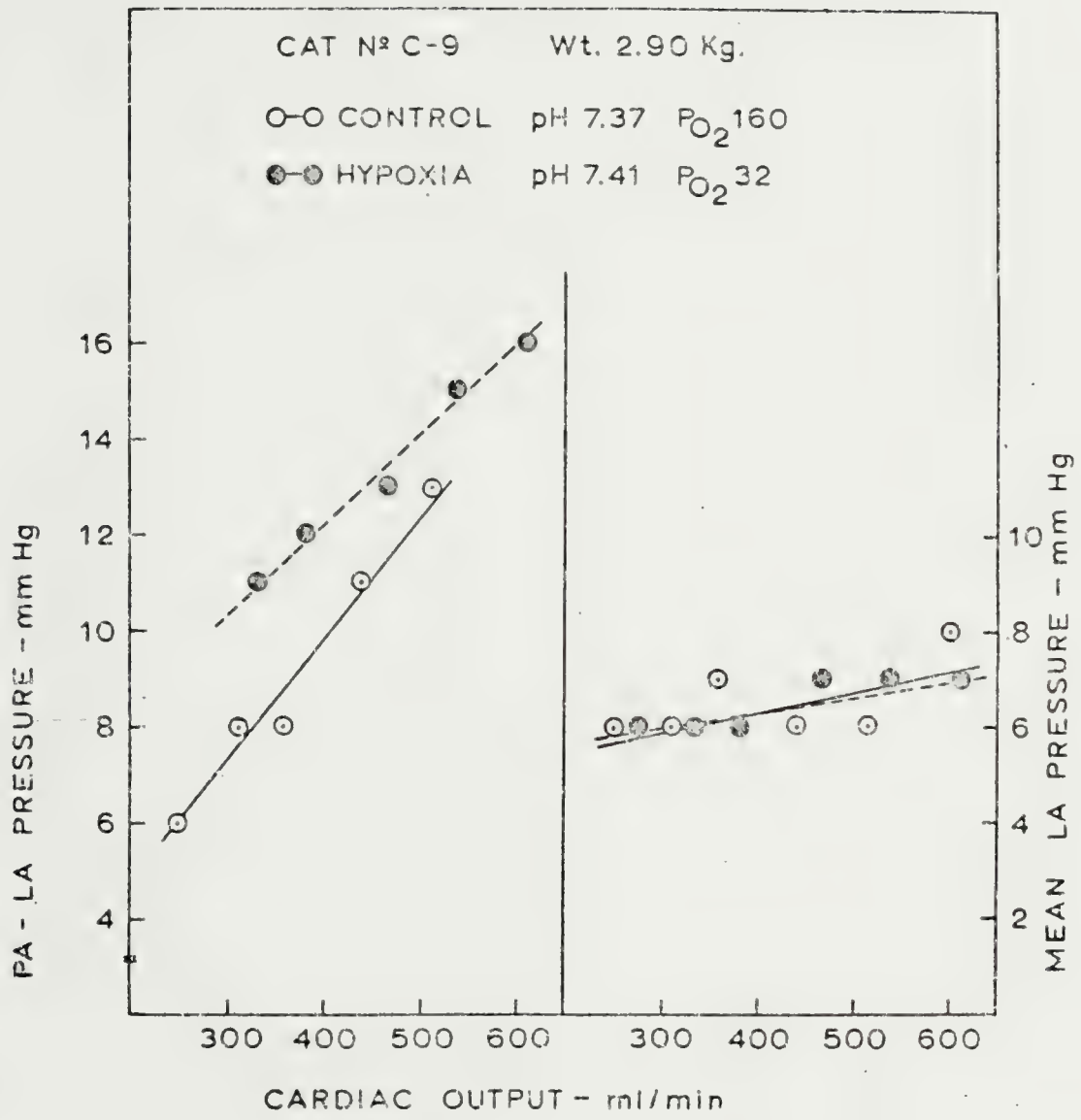

Fig. 10 Left atrial pressure-flow curves did not shift in response to hypoxemia and are shown virtually superimposed. Perfusion (PA-LA) pressure-flow curves paralleled the pulmonary artery curves and shifted to the pressure axis in response to hypoxemia.

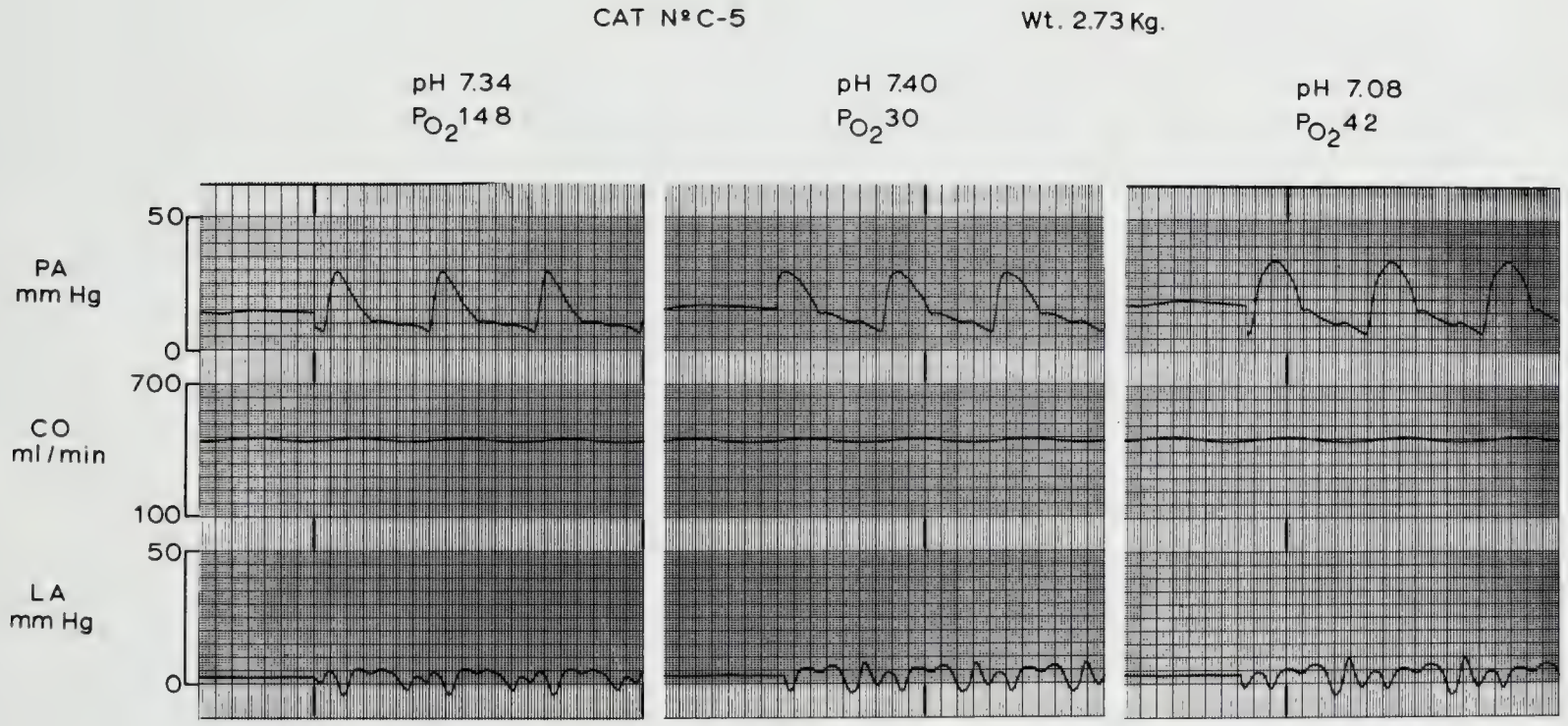

Fig. 11 Original traces obtained from a cat showing the relationship of PAP and LAP to Flow (C.O.) in response to hypoxemia. The tracings in the third panel were obtained during simultaneous hypoxemia and acidemia. Chart speed = 100 mm/sec. Aortic pressure 100 mm Hg.

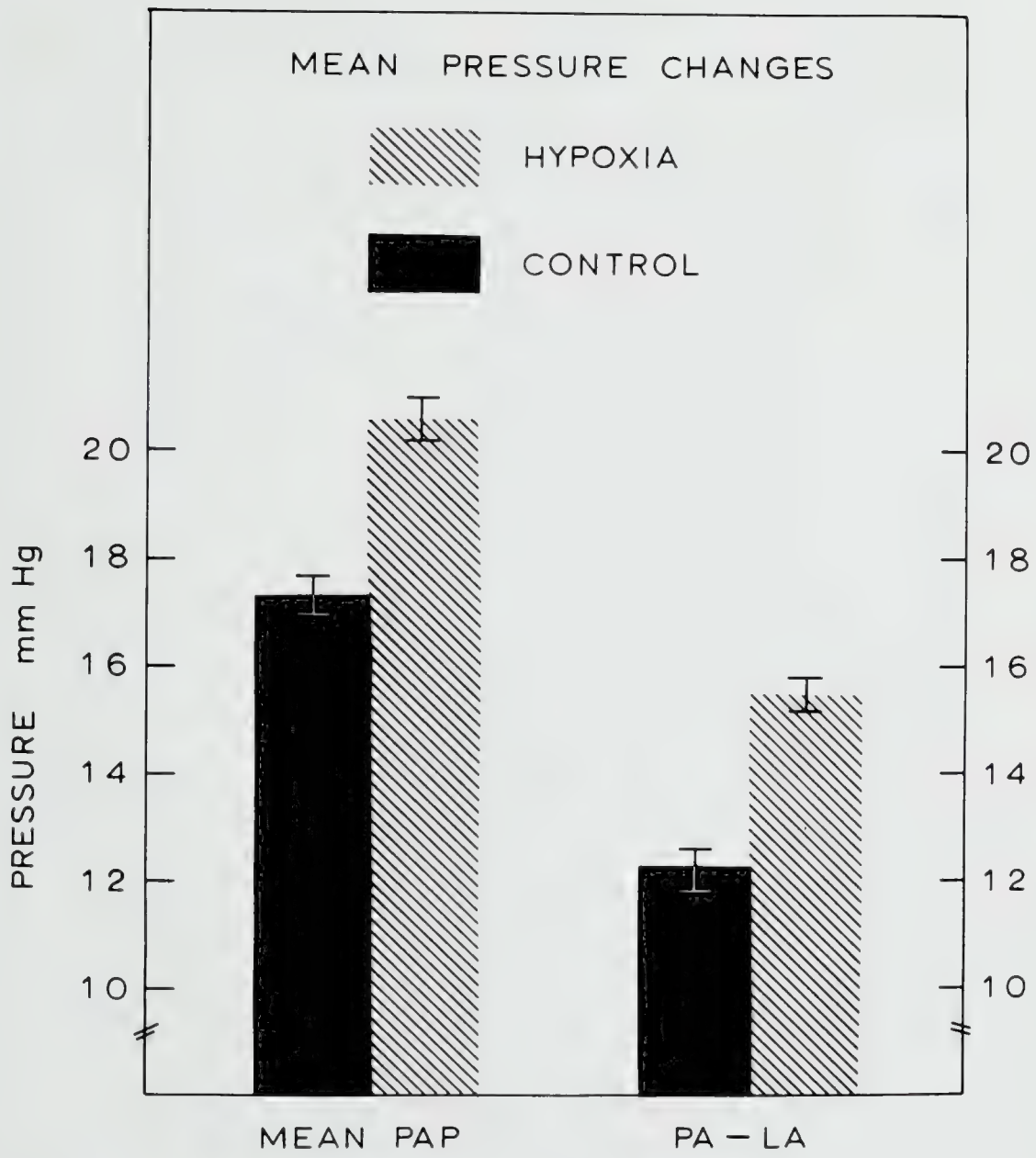

Fig. 12 Bar graph depicts the mean PA and PA-LA pressures along with their standard errors during both control and hypoxemic conditions.

C. HYPOXEMIA AND ACIDEMIA

Data are presented from a series of six experiments in which combined hypoxemia and acidemia were studied. These are from the fourteen successful preparations which comprised the previously noted hypoxemia study.

1. EFFECTS OF METABOLIC HYPOXEMIA AND ACIDEMIA ON PULMONARY ARTERY PRESSURE (PAP)

Arterial pH was reduced from control values of 7.35 - 7.45 by infusion of 1N lactic acid and was maintained at levels of 7.08 - 7.18. Simultaneously, arterial P_{O_2} was reduced from control levels of 100 mm Hg to a range of 30-45 mm Hg by means of the previously mentioned gas mixing device. The establishment of simultaneous hypoxemia and acidemia was associated with a shift of the pressure-flow curve toward the pressure axis. Throughout the range of cardiac outputs achieved, the pulmonary pressure for a particular flow was found to be increased during combined hypoxemia and acidemia as compared to control values. This response occurred uniformly in all animals tested. Upon correction of the hypoxemia and acidemia, mean pulmonary pressures were found to return to the original control values for a particular flow. A representative example of such a change in pressure-flow curves is shown in Figure 13. In Figure 14 four pressure-flow curves are presented and show that the combined stimuli effect a greater shift of the pressure-flow curve than either stimulus alone.

2. EFFECTS OF COMBINED HYPOXEMIA AND ACIDEMIA ON LEFT ATRIAL PRESSURE (LAP)

Left atrial pressure-flow curves during periods of simultaneous hypoxemia and acidemia were parallel to and slightly lower on the pressure axis that their control counterparts.

3. EFFECTS OF COMBINED HYPOXEMIA AND ACIDEMIA UPON PERFUSION PRESSURE (PA-LA)

Perfusion pressure-flow curves closely resemble the pulmonary artery pressure-flow curves of Figures 13 and 14. Throughout the range of cardiac outputs achieved, the perfusion pressure (PA-LA) for a given flow (C.O.) was increased during periods of combined hypoxemia and acidemia as compared to control values. This response was found uniformly in all animals and was entirely reversible.

4. EFFECTS OF COMBINED HYPOXEMIA AND ACIDEMIA ON PULMONARY VASCULAR RESISTANCE (PVR)

Pulmonary vascular resistance was calculated as previously indicated. When flow (C.O.) was plotted against resistance, a shift of the curve toward the resistance axis was found during conditions of simultaneous hypoxemia and acidemia as compared to the control. Thus there was increased vascular resistance for a given flow (C.O.) during periods of hypoxemia and acidemia as compared to the control. Similarly, when perfusion pressure (PA-LA) was plotted against resistance, this curve also shifted toward the resistance axis during periods of hypoxemia and acidemia as compared to the control. Thus, there was an increased vascular resistance for a given perfusion pressure during simultaneous hypoxemia and acidemia, and therefore, the amount of blood that could perfuse the lungs at a given perfusion pressure was decreased. A representative example of such curves is shown in Figure 15.

That these changes were reversible is demonstrated in Figure 16 which shows a sequential series of pressure measurements for a given flow from the pressure-flow curves of one experiment. Both pulmonary artery and perfusion pressure are represented graphically and it can be seen

that the effects of the combined stimuli was far greater than the effect of either hypoxemia or acidemia alone.

5. STATISTICAL ANALYSIS--COMBINED HYPOXEMIA AND ACIDEMIA

In order to standardize the data, pressures were taken from the pressure-flow curves at a flow rate of 125 ml/kg/min.

In Table 4 all data from the simultaneous hypoxemia and acidemia experiments have been compiled. The mean PA pressure during simultaneous hypoxemia and acidemia was found to be 21.2 mm Hg (S.E. = 1.75) as compared to a mean PA pressure during control periods of 15.9 mm Hg (S.E. = 1.25). In column ΔPA of Table 4, the PA during combined stimuli minus the PA control was calculated for each curve. The mean change in PA pressure was calculated to be 5.2 mm Hg (S.E. = 1.40). When the data for mean PA pressure was subjected to a "t" test, the p value $<.05$ was obtained confirming that the two groups are significantly different.

The mean LA pressure during stimulation with combined hypoxemia and acidemia was 3.2 mm Hg (S.E. = 0.40) as compared to a mean LA pressure during control periods of 4.3 mm Hg (S.E. = 0.56). These values are not significantly different ($p<.2$). As would be expected the data obtained regarding perfusion pressure (PA-LA) paralleled that concerning PA pressures. The mean PA-LA during simultaneous hypoxemia and acidemia was 18.0 mm Hg (S.E. = 1.98) as compared to control perfusion pressure 11.7 mm Hg (S.E. = 1.05). These values are significantly different ($p<.02$). The (PA-LA stimulus) minus (PA-LA control) was calculated for each curve and the mean ΔPA-LA was calculated to be 6.3 mm Hg (S.E. = 1.47).

The data from the hypoxemia-acidemia experiments may be compared with the data reported on hypoxemia as a single stimulus, since all the data

were obtained from different pressure-flow curves of the same experimental preparations.

The control PA pressure for the combined stimuli was 15.9 mm Hg (S.E. = 1.25) as compared to the control PA pressure for the hypoxemia experiments of 17.3 mm Hg (S.E. = 0.67), a difference of 1.4 mm Hg. The mean PAP during combined stimuli was 21.2 mm Hg whereas the mean PAP during hypoxemia alone was 20.6 mm Hg.

While this difference in PA pressures appears minimal, it is far more significant to evaluate the ΔPA pressures. Of note, the ΔPA during hypoxemia was 3.4 mm Hg whereas the ΔPA during hypoxemia and acidemia was 5.2 mm Hg.

When perfusion pressures were compared it is noted that the ΔPA-LA during hypoxemia was 3.2 mm Hg whereas the ΔPA-LA during hypoxemia and acidemia was 6.3 mm Hg. It is thus apparent that the shift of the pulmonary pressure-flow curve toward the pressure axis is greater during simultaneous hypoxemia and acidemia than during hypoxemia alone.

Table 4

DATA AND STATISTICAL ANALYSIS

Values from Pressure Flow Curves at 125 ml/kg Flow

		CONTROL MEAN PRESSURE			COMBINED ACIDEMIA & HYPOXEMIA MEAN PRESSURE				
ANIMAL	C.O.	PA	LA	PA-LA	PA	LA	PA-LA	ΔPA	ΔPA-LA
C-2	455	13.7	2.5	11.2	24.8	2.0	22.8	11.1	11.6
C-5	342	16.0	4.0	12.0	17.1	3.3	13.8	1.1	1.8
C-7	342	17.7	3.9	13.8	21.3	2.9	18.4	3.6	4.6
C-8	362	12.5	3.5	9.0	17.8	3.0	14.8	5.3	5.8
C-9	362	14.7	6.0	8.7	18.3	5.0	13.3	3.6	4.6
C-10	342	21.0	5.8	15.2	27.7	3.0	24.7	6.7	9.5
Mean		15.9	4.3	11.7	21.2	3.2	18.0	5.2	6.3
Standard Deviation		3.07	1.36	2.58	4.29	.99	4.86	3.44	3.59
Standard Error		1.25	.56	1.05	1.75	.40	1.98	1.40	1.47
"T" Test					$p < .05$	$p < .2$	$p < .02$		

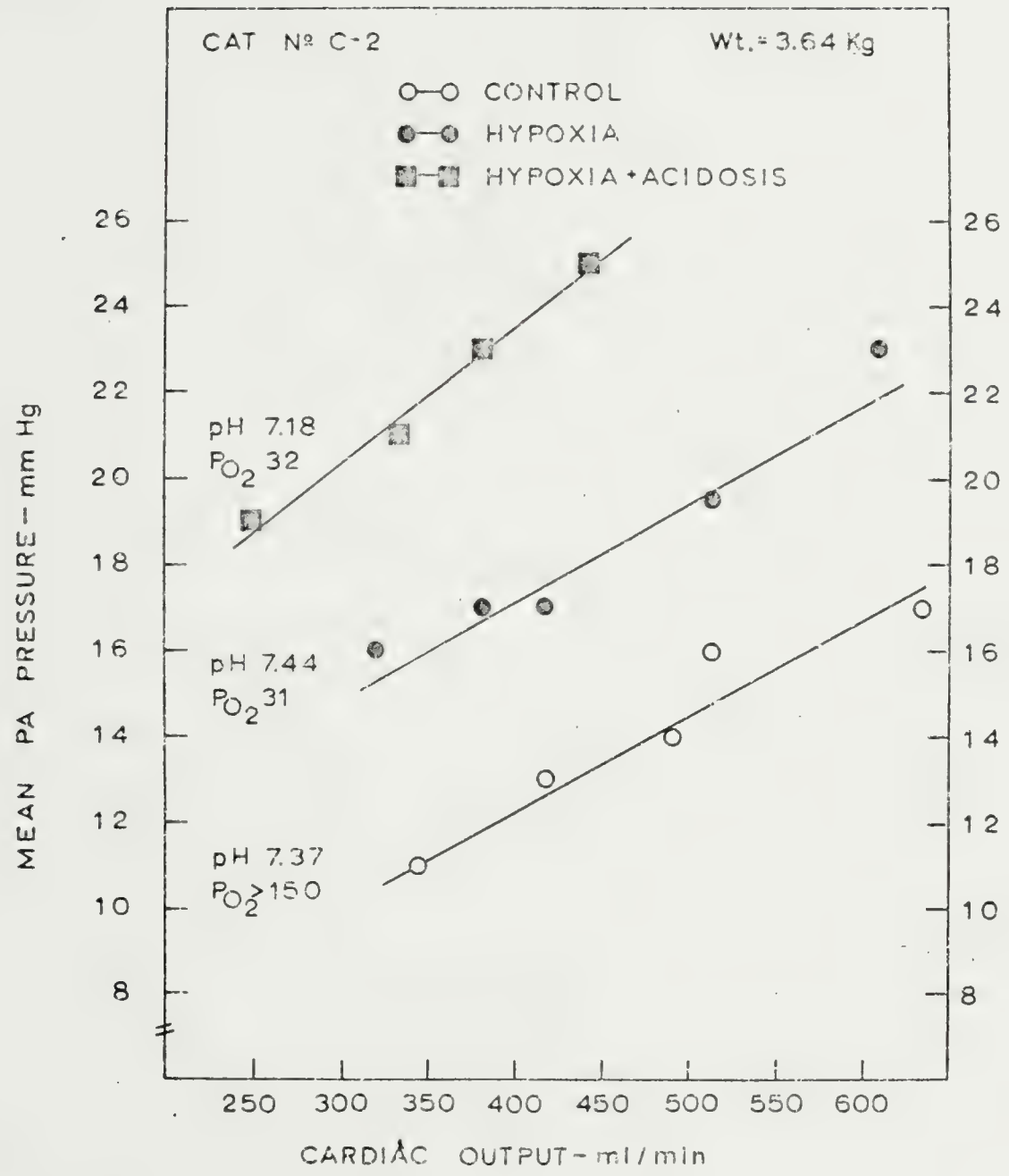

Fig. 13 Pulmonary artery pressure-flow curves demonstrating a shift of the curve toward the pressure axis in response to hypoxemia as well as to simultaneous hypoxemia and acidemia.

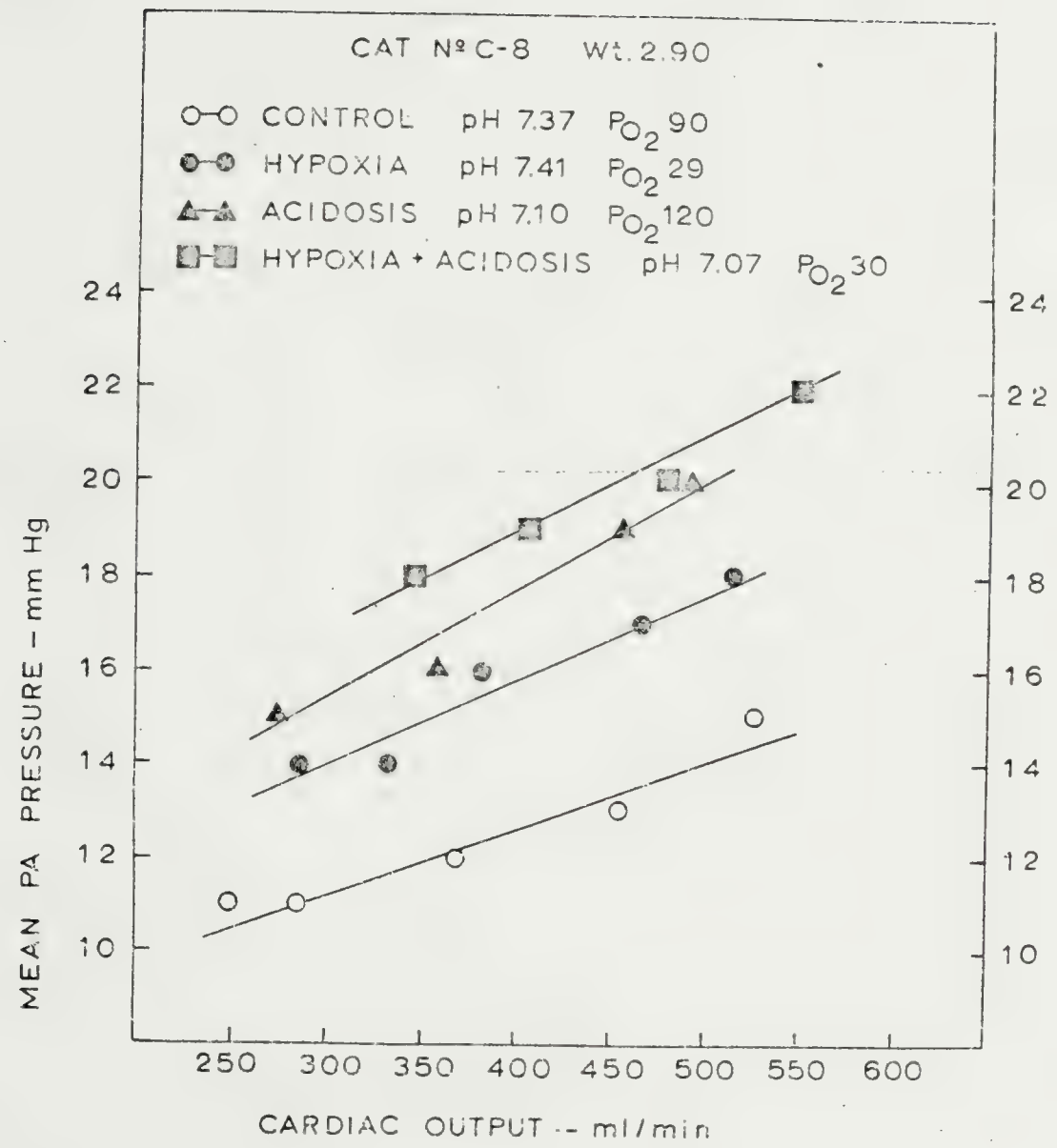

Fig. 14 Pulmonary artery pressure-flow curves showing a shift of the curve toward the pressure axis in response to either hypoxemia or acidemia. Of note, the shift of the curve is greater in response to a combination of hypoxemia and acidemia than in response to either stimulus alone.

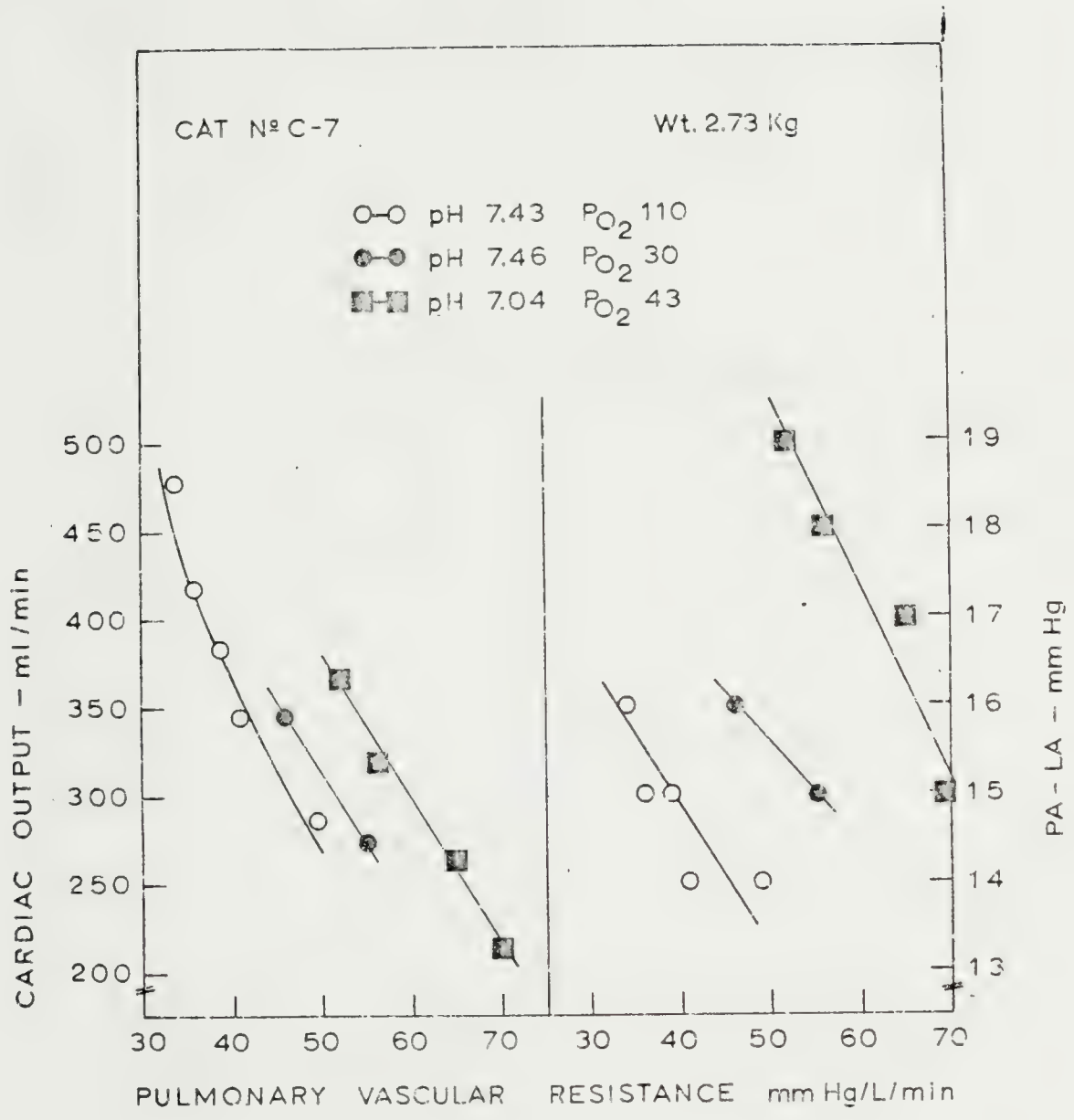

Fig. 15 Pulmonary vascular resistance is plotted against both cardiac output and perfusion pressure. In both instances the curve shifts toward the resistance axis in response to hypoxemia. Of note, there is a greater shift of the curve in response to simultaneous hypoxemia and acidemia than in response to hypoxemia alone.

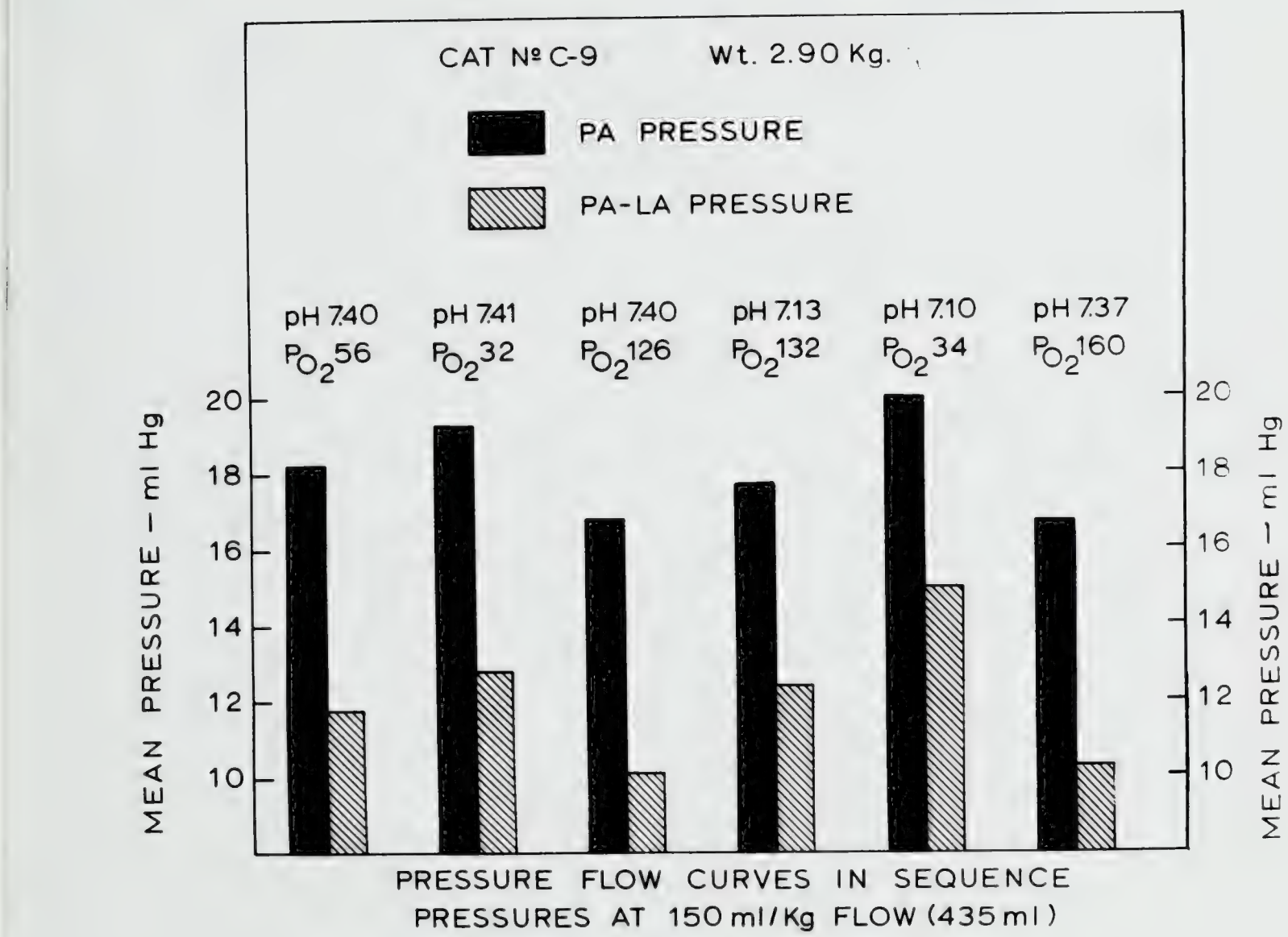

Fig. 16 Bar graph depicts mean PA and PA-LA pressures at a C.O. = 150 ml/kg/min. for a sequential series of pressure-flow curves. Of note, PA and PA-LA pressures respond in a graded fashion to increasing degrees of hypoxemia. The PA and PA-LA pressures are also increased in response to acidemia. The response to combined hypoxemia and acidemia is greater than that to either stimulus alone. Reversibility of the response is shown by the return to the baseline of the control curves.

D. SYMPATHETIC STIMULATION

Data are presented from a series of six technically successful preparations in a total of twelve. An additional thirty cats were used as donor animals to provide blood for the extracorporeal circuits.

The episodic production of CNS ischemia without changing the venous return to the heart (see Preparations and Procedures) resulted in a generalized autonomic discharge characterized by an initial bradycardia followed by a tachycardia, a rise in peripheral resistance, and an increase in systemic pressure, occasionally accompanied by a fall in cardiac output. Atropine, 1 mg IV, was administered to block the vagal effects upon the heart, thereby greatly reducing the initial bradycardia. The remaining effects were attributed to the sympathetic portion of the autonomic nervous system. Only animals found to be reflexic as judged by the afore-mentioned criteria are herein reported. Pressure-flow curves were taken before, during and after episodic ischemia of the CNS. The CNS was rendered ischemic for intervals of less than three minutes.

1. EFFECTS OF SYMPATHETIC STIMULATION ON PULMONARY ARTERIAL PRESSURE (PAP)

Sympathetic stimulation achieved by means of CNS ischemia was associated with no shift of the pulmonary pressure-flow curve. Throughout the range of cardiac outputs achieved, the mean pulmonary arterial pressure for a particular flow remained unchanged from control during sympathetic stimulation. With resumption of CNS perfusion and reversal of the cardiac and systemic vascular responses, the pulmonary pressure-flow curve was unaltered. A representative example from these experiments is shown in Figure 17. The mean aortic pressure during the course of these experiments was held constant at 100 mm Hg, as was the brachiocephalic pressure during

periods of CNS perfusion. Arterial pH ranged from 7.35 to 7.45 and P_{O_2} was held at values of 100 mm Hg or greater.

2. EFFECTS OF SYMPATHETIC STIMULATION ON SYSTOLIC AND DIASTOLIC PAP

Systolic pulmonary pressures were universally higher during the periods of CNS ischemia as compared to control values. Diastolic pressures during sympathetic stimulation were lower than control in four of the eight pressure-flow curves studies, equal in one, and higher in three. Figure 17 represents a typical experiment in which the systolic, mean and diastolic pressure-flow curves are depicted.

3. EFFECTS OF SYMPATHETIC STIMULATION ON LEFT ATRIAL PRESSURE (LAP)

Left atrial pressure-flow curves were practically identical during sympathetic stimulation and control periods. Figure 18 (right panel) shows an LA pressure-flow curve of a representative experiment and demonstrates the relationship of the curves during both control and sympathetic stimulation conditions.

4. EFFECTS OF SYMPATHETIC STIMULATION ON PERFUSION PRESSURE (PA-LA)

Since the LA pressure-flow curve was found to remain at control levels during sympathetic stimulation, the relationship of perfusion pressure (PA-LA) to flow was similar to that of PAP to flow. Throughout the range of cardiac outputs achieved, the perfusion pressure (PA-LA) for a given flow (C.O.) was the same during sympathetic stimulation and control periods. Figure 18 demonstrates representative curves.

5. EFFECTS OF SYMPATHETIC STIMULATION ON PULMONARY VASCULAR RESISTANCE (PVR)

Pulmonary vascular resistance was again calculated according to the formula $\frac{\text{PA-LA}}{\text{flow}} \times 1000 = \text{Resistance Units (mm Hg/L/min)}$. When flow (C.O.) was plotted against resistance (PVR) the curves did not shift during

sympathetic stimulation, and there was no change in vascular resistance for a given flow (Fig. 19--left panel). Similarly, when pulmonary perfusion pressure (PA-LA) was plotted against resistance there was no shift of the curve during sympathetic stimulation (Fig. 19--right panel). Thus, no increase in vascular resistance for a given perfusion pressure could be demonstrated during sympathetic stimulation. Therefore, the amount of blood flow that could perfuse the lungs at a given perfusion pressure did not decrease in response to sympathetic stimulation.

Original traces from a representative experiment are depicted in Figure 20. The tracings in the control panel were obtained while the CNS was being perfused at 100 mm Hg pressure. Blood pH was maintained at levels between pH 7.35-7.45 and P_{O_2} was greater than 100 mm Hg. The tracings during sympathetic stimulation (right panel) were obtained after 90 seconds of CNS ischemia in an atropinized animal. With cardiac output, LAP and systemic pressure held constant, sympathetic stimulation resulted in an increased heart rate, but no change in mean pulmonary pressure. Pulmonary systolic pressure increased and diastolic pressure decreased during this period. Thus, there was a marked change in the pulse pressure with no change in flow or perfusion pressure.

Sympathetic blockade was achieved with TEAC infused IV to establish that the hemodynamic changes were of sympathetic origin. Traces from the same animal following TEAC infusion are shown in Figure 21. It will be noted that the production of CNS ischemia failed to produce a change in heart rate, cardiac output, PAP, LAP, or AOP. Noteworthy, also, is the fact that there was no demonstrable change in the PA pressure contour.

6. STATISTICAL ANALYSIS--SYMPATHETIC STIMULATION

To standardize the data, pressures were taken from the pressure-flow curves at a flow rate of 100 ml/kg body weight. This was selected because it could be applied to all the pressure-flow curves obtained and required few extrapolations.

All data from the sympathetic stimulation experiments have been compiled in Table 5. The mean PA pressure after sympathetic stimulation was 18.68 mm Hg (S.E. = 1.73), compared to the mean PAP during control periods of 18.83 mm Hg (S.E. = 1.89). The calculated $p<.9$ indicates that these populations do not differ significantly. The PA systolic was 41.0 mm Hg (S.E. = 2.33), compared to 37.0 mm Hg (S.E. = 2.42) during control periods, with a calculated $.9>p<.8$. The PA diastolic was 16.8 mm Hg (S.E. = 1.46) during sympathetic stimulation, and 17.6 mm Hg (S.E. = 1.34) during the control periods, with a calculated $.8>p<.7$. Thus, the mean PAP did not vary significantly during experimental periods from control values. The slight increase in PA systolic and decrease in PA diastolic during ischemic stimulation periods was not statistically significant.

The mean LA pressure during sympathetic stimulation was 4.43 mm Hg (S.E. = 0.98) compared to the mean of 4.78 mm Hg (S.E. = 0.85) during control periods. The calculated $.8>p<.7$ was also not statistically significant.

The mean PA-LA during sympathetic stimulation was 14.25 mm Hg (S.E. = 1.40) and did not differ significantly from control values of 14.10 mm Hg (S.E. = 1.43) ($p<.9$).

Table 5

DATA AND STATISTICAL ANALYSIS

Values from Pressure Flow Curves at 100 ml/kg Flow

		CONTROL					SYMPATHETIC STIMULATION				
	C.O.	PAM	PAS	PAD	LA	Sub PA-LA	PAM	PAS	PAD	LA	Sub PA-LA
B-14 (2)	336	19.0	27.0	11.0	5.0	14.0	18.6	35.4	9.8	3.8	14.8
(3)	336	(14.6)	(20.0)	(8.8)	(4.8)	9.8	(15.2)	(31.4)	(6.4)	(2.6)	12.6
(4)	336	14.4	23.0	8.0	4.0	4.0	14.2	29.6	7.0	4.0	10.2
B-16 (1)	273	14.4	24.4	13.0	6.0	11.4	17.6	25.6	13.0	6.0	11.6
B-17 (1)	300	25.0	33.0	16.0	8.0	17.0	(23.0)	(38.4)	(16.8)	(9.6)	13.4
B-19 (1)	290	26.6	36.6	17.6	4.8	21.8	25.0	35.4	15.6	(3.0)	22.0
B-20 (2)	336	11.6	21.2	7.0	-.4	12.0	11.8	21.4	7.4	.4	11.4
B-21 (1)	273	22.0	37.0	13.0	6.0	16.0	24.0	41.0	14.0	6.0	18.0
Total	2480	150.6 8	222.20	94.4	38.2	112.4	149.40 8	258.20	90.0	35.4	114.0
Mean	310	18.83	27.78	11.8	4.78	14.1	18.68	32.28	11.25	4.43	14.25
Mean		18.83	27.78	11.8	4.78	14.1	18.68	32.28	11.25	4.43	14.25
Data Range Low		11.6	20.0	7.0	-.4	9.8	11.8	21.4	6.4	.4	10.2
High		26.6	37.0	17.6	8.0	21.8	25.0	41.0	16.8	9.6	22.0
n		8	8	8	8	8	8	8	8	8	8
Standard Deviation		5.35	6.85	3.80	2.41	4.06	4.89	6.59	4.12	2.77	3.95
Standard Error		1.89	2.42	1.34	.85	1.43	1.73	2.33	1.46	.98	1.40
"T" Test							p<.9	p<.8	p<.7	p<.7	p<.9

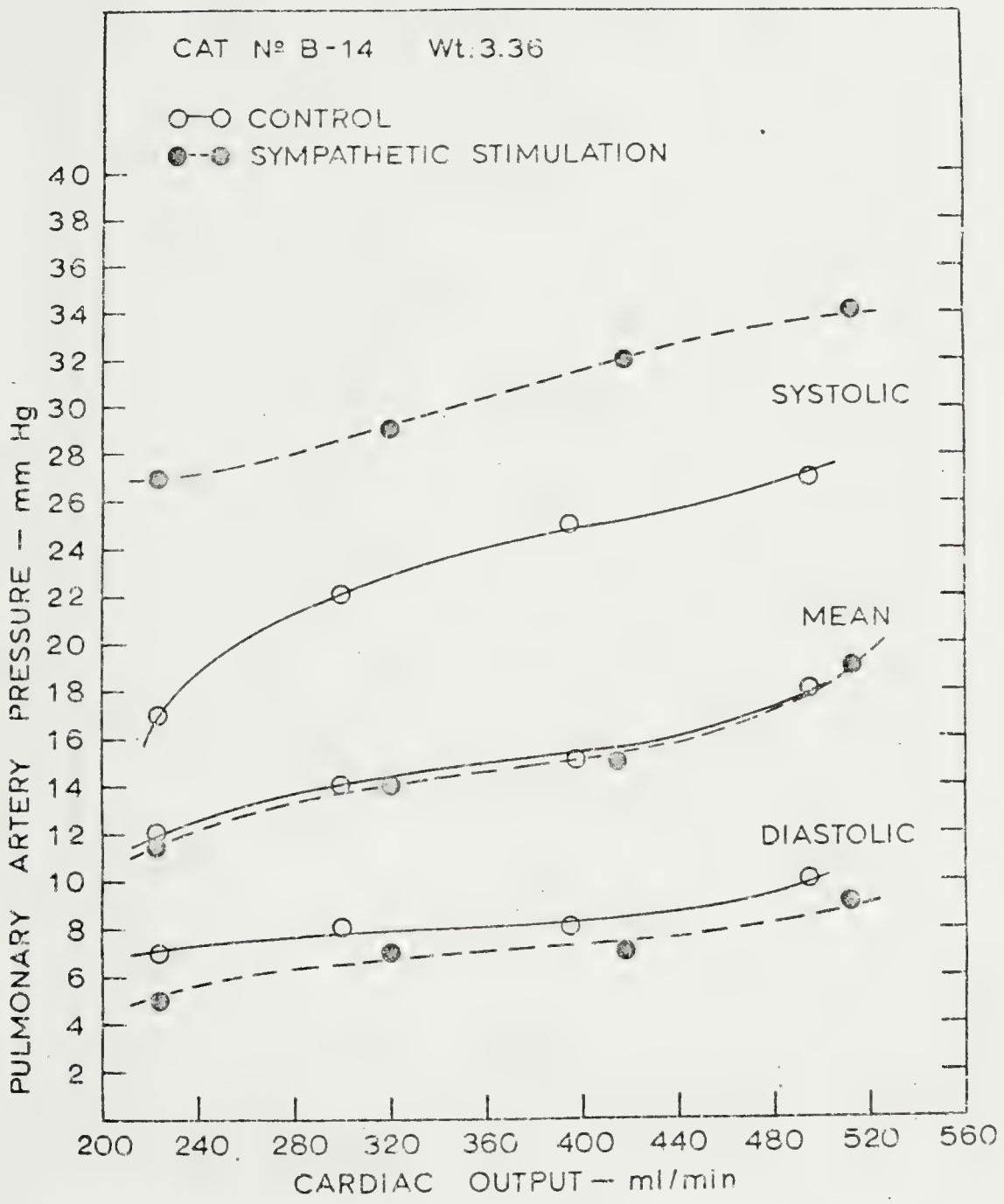

Fig. 17 Pulmonary artery pressure-flow curves showing no shift of the mean pressure curve in response to sympathetic stimulation. Of note, the systolic pressure flow curve is elevated and the diastolic pressure flow curve depressed in response to sympathetic stimulation.

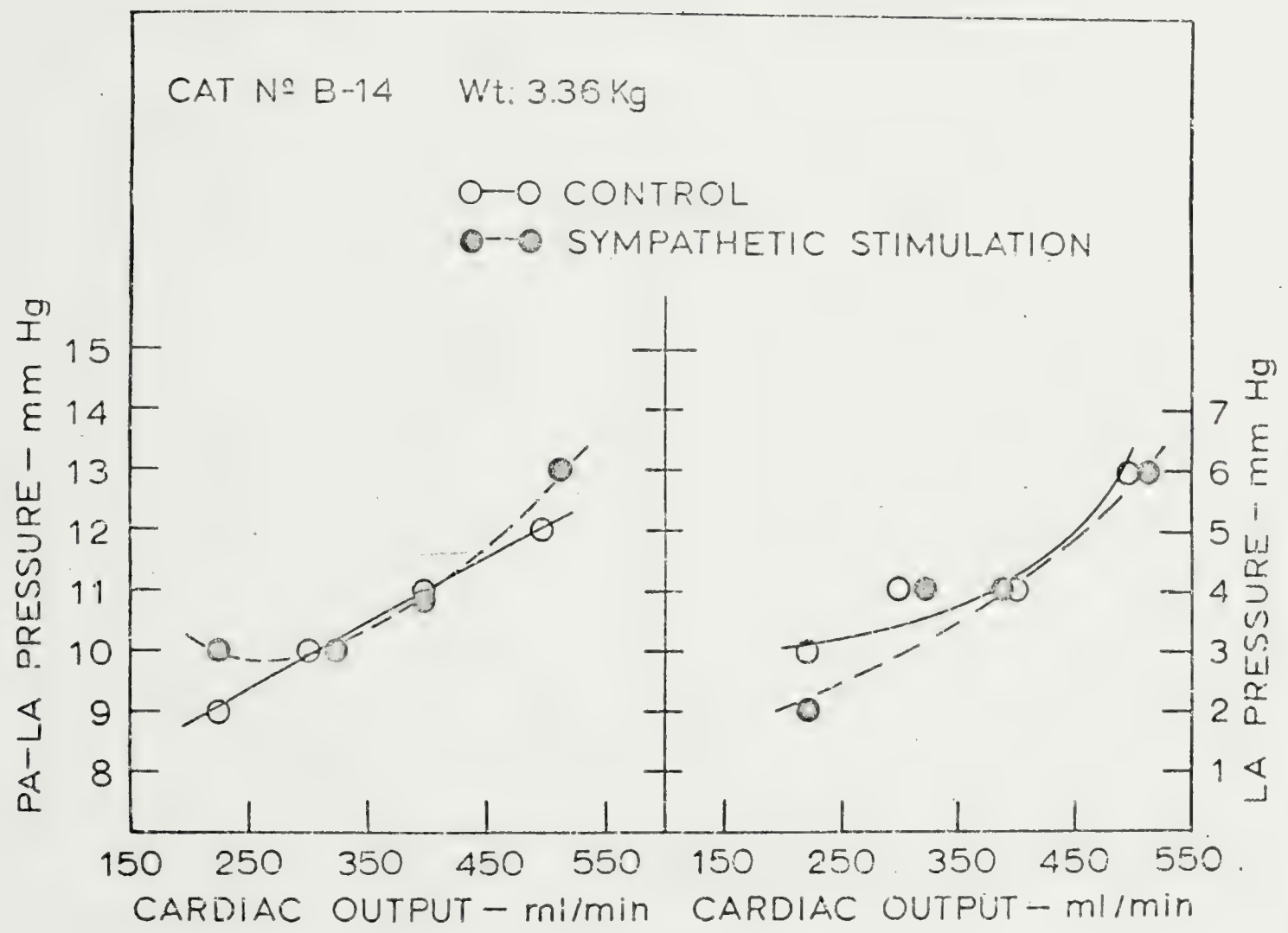

Fig. 18 Left atrial and perfusion pressure-flow curves are depicted. There is no shift of the curves in response to sympathetic stimulation.

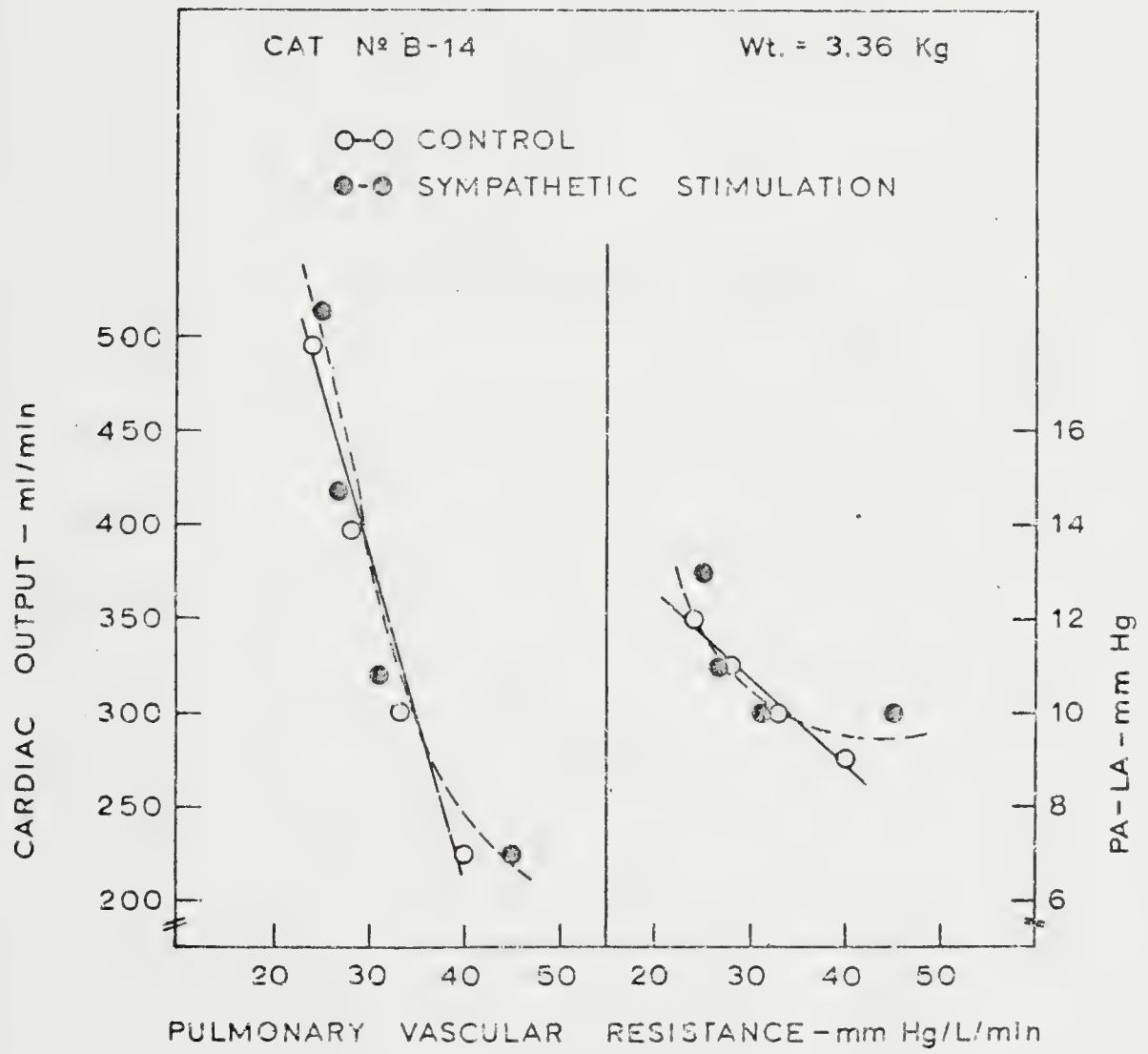

Fig. 19 Pulmonary vascular resistance is plotted against both cardiac output and perfusion pressure. In both instances there is no shift of the curve toward the resistance axis in response to sympathetic stimulation.

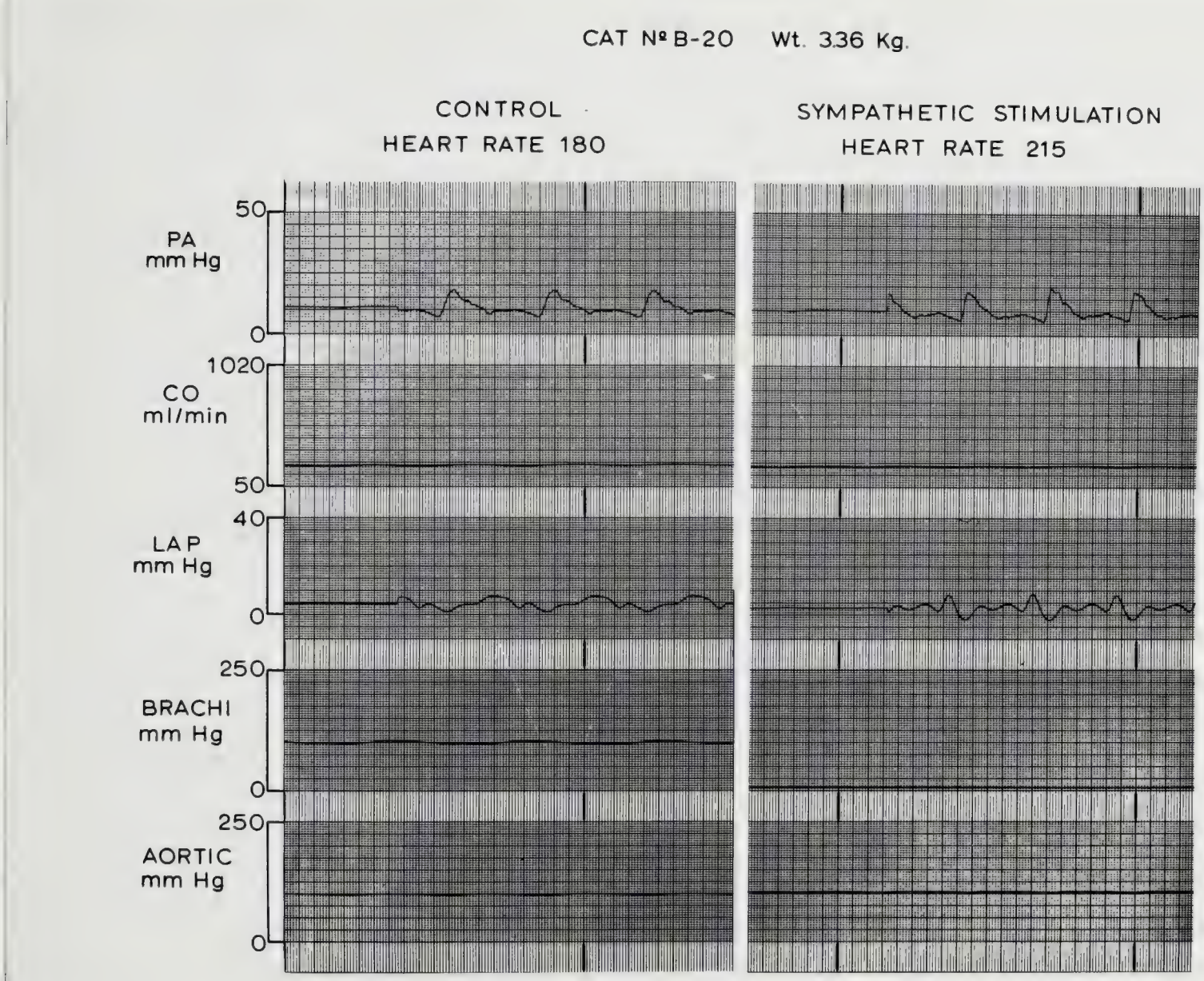

Fig. 20 Original traces obtained from a cat showing the relationship of PAP and LAP to Flow (C.O.) in response to sympathetic stimulation resulting from CNS ischemia. Aortic pressure was constant at 100 mm Hg. Note the trachycardia in response to sympathetic stimulation but no increase in mean PAP or LAP. The configuration of the PA tracing does change with sympathetic stimulation.

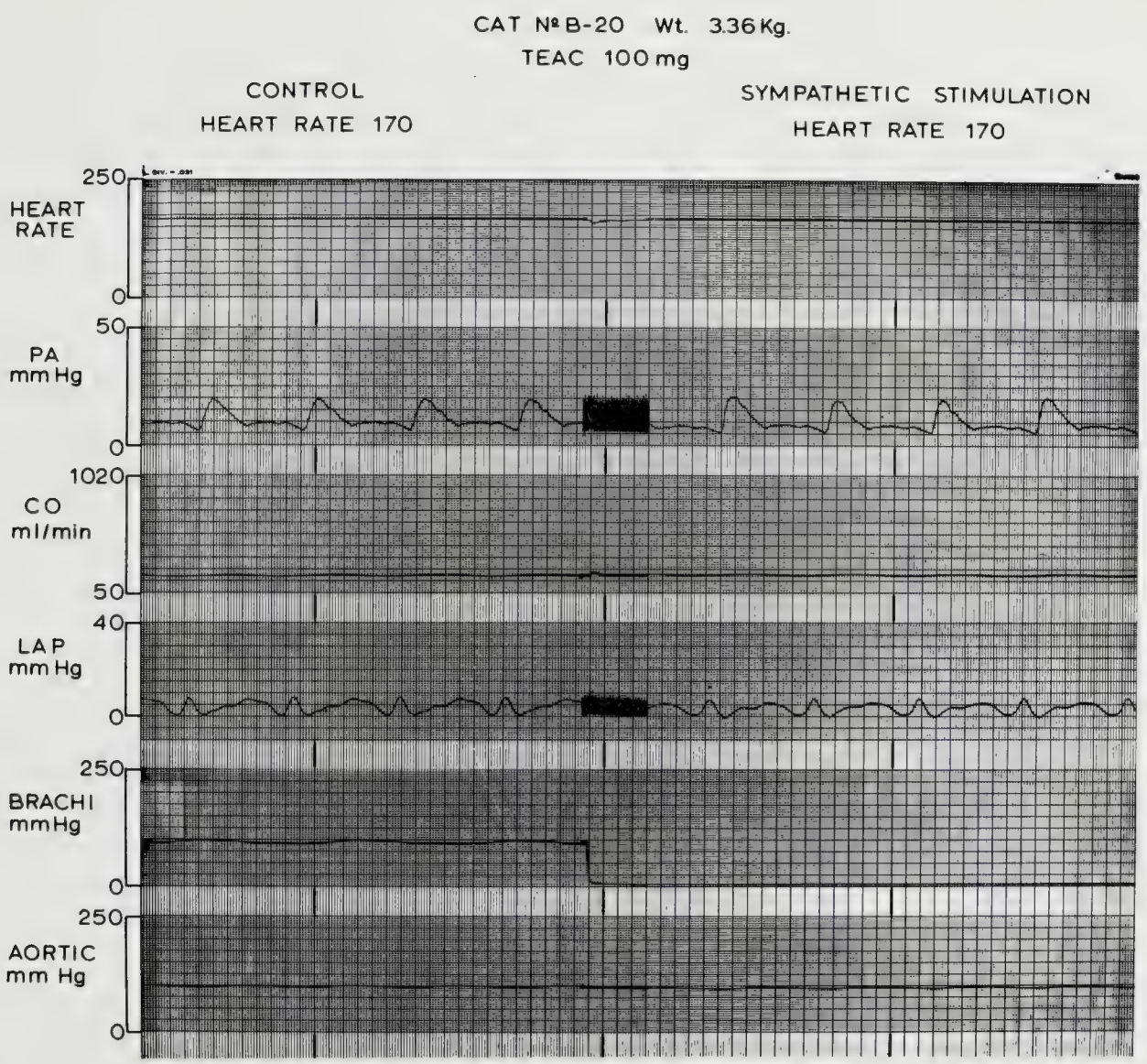

Fig. 21 Original traces obtained from a cat showing the relationship of PAP and LAP to C.O. during sympathetic stimulation following the administration of TEAC 100 mg. Aortic pressure cardiac output and heart rate did not change in response to sympathetic stimulation subsequent to blocking.

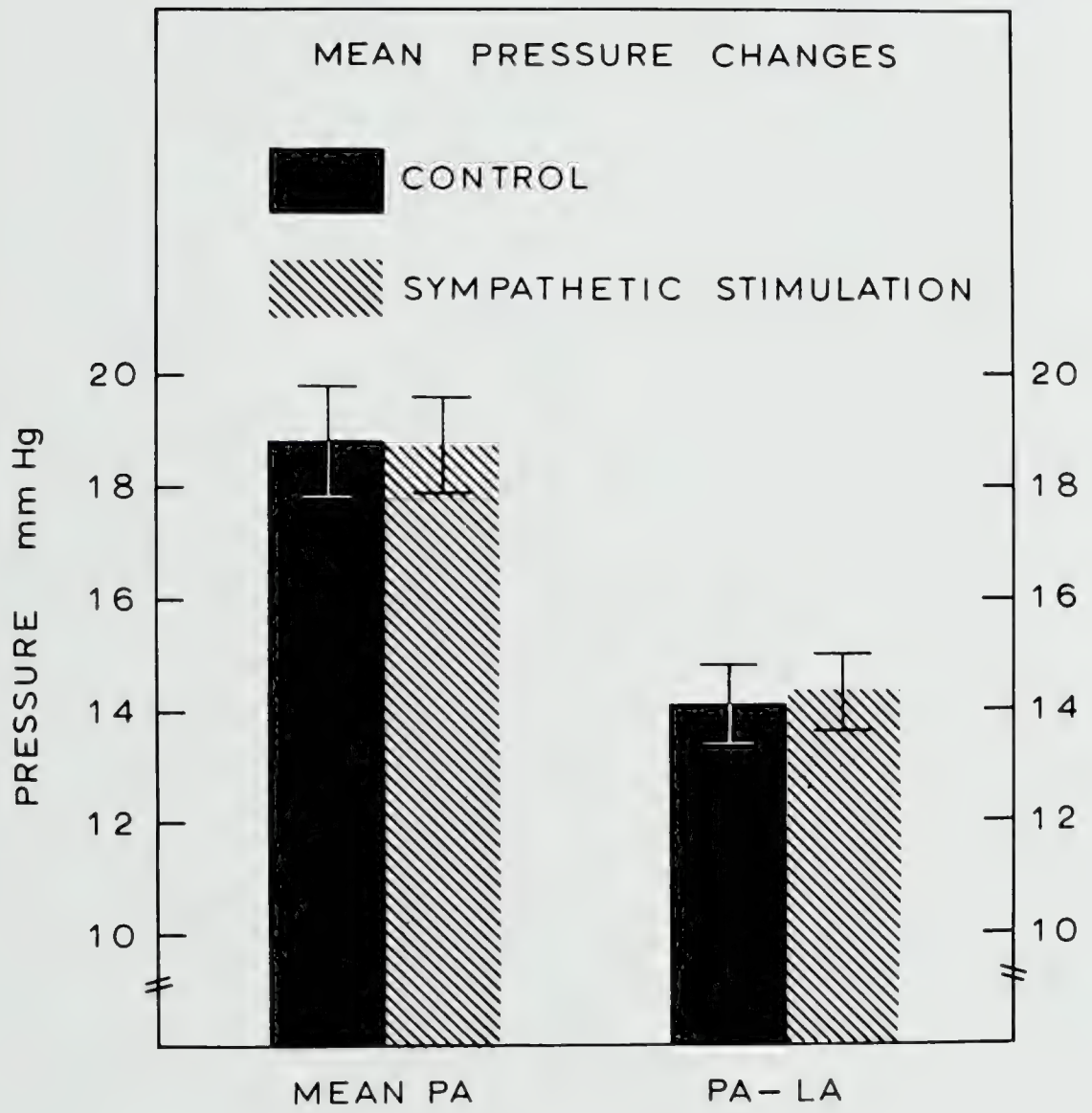

Fig. 22 Bar graph depicts the mean PA and PA-LA pressures along with their standard errors during control periods and following sympathetic stimulation.

V. REVIEW OF THE LITERATURE

Whereas Beutner [13] was reportedly the first to record pulmonary arterial pressures, Openchowski is cited by Nahas[85] as having first described changes in pulmonary hemodynamics with hypoxia. Wood[117], in 1902, demonstrated a rise in PAP in dogs during asphixia, and Plumier[92], in 1904, reported a pulmonary pressor response due to hypoxia. However, remarkably little research was devoted to this subject in the early twentieth century until the classic work of Von Euler and Liljestrand in 1946.[43] Stimulated by their work on the systemic vasculature, they pursued the question of whether or not the pulmonary arterial pressure was regulated in a similar fashion to the systemic pressure, and studied the effects of several factors including hypoxia. Liljestrand observed an increase in PAP when cats were respirated on 10% O_2 in N_2 and noted the effect was unaltered by vagotomy or sympathectomy, concluding that it "...must be regarded as a direct effect on the lung vessels." They postulated that "the regulation of the pulmonary blood flow is mainly mediated by the local action of the blood and alveolar gases leading to an adequate distribution of the blood through the various parts of the lung according to the efficiency of aeration."[43] In other terms, they believed that a decreased alveolar P_{O_2} caused a local vasoconstriction, and thus redistribution of the pulmonary blood flow to better ventilated regions.

Motley,[82] in 1947, studied the effects of acute episodes of hypoxia upon the pulmonary artery pressure of an unanesthetized man by means of right heart cardiac catherization. He reported a reversible increase in

PAP from a normal baseline coincident with a decrease in cardiac output and a calculated increase in resistance.

Westcott,[114] in 1951, was stimulated by the fact that Liljestrand[43] had not measured the cardiac output when studying the effects of 10% O_2 on pulmonary circulation of cats. Using a technique designed to measure "capillary pressure"[56] by means of right heart catherization, Westcott examined the effects of acute hypoxia upon "pulmonary arteriolar resistance"[114] in normal unanesthetized men. In these experiments mean PAP was found to increase 24% in response to breathing 13% O_2 and this effect was reversible. Interestingly, there was no significant change in cardiac output or capillary pressure. In each subject the calculated PVR (actually a pulmonary arteriolar resistance) increased with hypoxia. Westcott concluded that anoxia caused an increase in PVR by means of vasoconstriction.

Nahas,[86] in 1951, was able to study the effects of acute hypoxia upon PAP and LAP in unanesthetized dogs. In these experiments angiostomy cannulae were placed over the PA and LA at thoracotomy, and after recovery, catheters for pressure measurements were inserted. Cardiac output was measured indirectly by means of O_2 consumption. Nahas found an increase of 28% in mean PAP with no change in LAP during breathing 8% O_2. Concurrently cardiac output decreased 30% and the calculated PVR increased 123%. Nahas concluded that vasomotion in response to hypoxia caused the increase PAP. In the same year Atwell[4] described experiments in which the lungs of anesthetized animals were ventilated separately, one with air, while the other was allowed to rebreathe expired air. In these experiments there was a shift in blood flow to the air breathing lung when the other

lung was rebreathing, however, one half of these animals showed no response.

Aviado[6], in experiments performed on anesthetized dogs, found an increase in PAP in a delayed response to hypoxia. However, in these experiments, there was a marked increase in cardiac output which could explain the increase in PAP. Aviado was led to conclude that the pulmonary vessels responded as did systemic by dilation when subjected to anoxia. (A conclusion he subsequently reconsidered)

Stroud[107] described an increase in PVR with hypoxia, but this response was said not to occur after sympathectomy which is supportive for the theory that the response is in some way dependent on the sympathetic nerves. However, Von Euler[43] and Dirksen[36] found no change in the pressor response after sympathectomy.

Siebens,[103] in 1955, attempted to differentiate between the effects of hypoxia and changes in flow which might be secondary to hypoxia, upon pulmonary vascular resistance. In studies using young men with bronchiectasis or sarcoid he demonstrated an increasein PAP with the increase flow of exercise. Hypoxia, added to exercise, greatly increased PAP and, whereas the calculated resistance decreased with exercises, it increased in the presence of hypoxia. Measurements of LA pressure were not made in this study, however. Siebens demonstrated the pressor effects of hypoxia and the increased PVR and concluded that they were due to constriction of the pulmonary vessels.

Liljestrand,[68] in experiments performed in 1958 on isolated perfused cat lungs, demonstrated that an increase in pH, caused by excess loss of CO_2 resulted in a rise in pulmonary perfusion pressure. Perfusion of the

lung with blood containing lactic acid produced a similar rise in perfusion pressure, however, the decrease in pH during such a procedure was slight. Liljestrand found that hypoxia in this preparation caused a liberation of lactic acid which might lower the blood pH. He describes a relationship between decrease in pH and rise in pulmonary artery pressure. Further support for this thesis that lactic acid plays a fundamental role in the rise of pulmonary pressure during hypoxia was the observation that the use of monoiodoacetic acid to stop the liberation of acetic acid results in a loss of the pressor response to hypoxia. Liljestrand was led to conclude that P_{O_2} served to regulate the pulmonary circulation by means of varying the pH, thus causing vasoconstriction and subsequent decrease of flow.

It was the conclusion of Liljestrand that stimulated Enson[42] et al. to undertake a study of the effects of changing blood pH on the pulmonary artery pressures of patients with chronic pulmonary disease. In this study using cardiac catherization data, Enson describes a relationship between hydrogen ion concentration and the pulmonary pressor response. The fall in (H+), (increased pH) was concluded to cause vasodilation on the basis that the pulmonary artery pressure showed no change, or actually decreased despite significant increases in cardiac output. The impression that the vascular bed had increased in capacity was strengthened by the finding of an increased pulmonary blood volume. In a similar study Enson describes an increased PAP and increased CO in patients with chronic pulmonary disease subjected to hypoxia. When Tris was administered with a resultant decrease in arterial oxygen saturation and a rise in pH, there was no increase in PAP. Enson concludes that a rise in pH may

prevent the pressor response to hypoxia in these patients. Bergofsky[10] et al. in a study of normal patients could not demonstrate that Tris buffer changed the pressor response to hypoxia, although his data concerning arterial oxygen saturation and pH were the same as Enson's. It was unclear, however, whether the pressor response to hypoxia could only be modified by a rise in pH in diseased circulations of if a greater rise in pH would be necessary to demonstrate this phenomenon.

In a more direct fashion, Enson[42] infused 0.3M HCl into a patient who had shown a decrease in PAP in response to Tris, and demonstrated that acidosis resulted in a rise of PAP. When data from such experiments were subjected to complex statistical analysis, mean PAP was shown to correlate better with both (H+) and oxygen saturation than with either of these parameters alone. The data indicated that in relative alkalosis the pressor response to hypoxia is mollified, whereas in relative acidosis the pressor response to hypoxia is exaggerated. On the basis of these experiments Enson speculated that "...hydrogen ion concentration and hypoxia are interacting stimuli, one either facilitating or inhibiting the effects of the other at the level of vascular smooth muscle."[42] Enson recognized the similarity of this concept to that of Liljestrand.

Rudolph and Yuan[99] undertook a study to determine the effects of varying degrees of hypoxia upon the pulmonary circulation of newborn calves. The experimental design used is of interest in that it called for an open chest procedure in anesthetized animals in order to gain access to and cannulate the great vessels. Then the chest was closed in layers and cannulas externalized as in a chronic preparation, but the experiments were performed in the acute period while the animals continued

under anesthesia. In these investigations, acidosis during 100% oxygen inspiration led to an increase in mean PAP with a coincident decrease in pulmonary flow, and LAP. Calculated PVR increased. The response to hypoxia varied according to the pH. At pH 7.3 or greater hypoxia resulted in minor decreases in flow and increases in PAP, but hypoxia caused significant increases in PAP at pH less than 7.3. Again, PVR increased and the magnitude of the increase with hypoxia was found to vary with the degree of acidosis. The pressor response and PVR were found to vary in magnitude with the degree of hypoxemia, and Rudolph demonstrated a relationship of pH and P_{O_2} levels, small changes in pH result in large percentage increases in PVR. The fact that bilateral sympathectomy had no effect on the pulmonary vascular response to acidosis or hypoxia led Rudolph[99] to postulate that such responses are local rather than reflex phenomena.

Bergofsky[10] and Fishman demonstrated that the pressor response to acidosis is similar whether it be acidosis of respiratory or metabolic origin. They did not correlate the degree of acidosis with the magnitude of this pressor response, however.

Wilcox,[115, 116] using a separate perfusion of the greater and lesser circuits, reported that alveolar hypoxia had a varied but insignificant effect upon PAP while systemic hypoxia resulted in an increase in PAP and PVR.

Harvey,[55] in 1965, using a mathematical analysis, attempted to predict the mean PAP on the basis of P_{O_2} and (H+) and compare these predictions

with observed values in 43 patients with chronic obstructive pulmonary disease. She was able to predict pulmonary pressure quite accurately in these patients, but the pulmonary pressure of normal subjects could not be predicted accurately by this method. A graphic representation of this data revealed that at low (H+) the pulmonary vasculature is relatively insensible to hypoxia whereas during acidosis, it is extremely responsive to hypoxia. Harvey concluded that "variations in PAP, as observed in patients with obstructive disease of the lungs, can best be ascribed to the interactions of alveolar oxygen tension and blood hydrogen ion concentration upon muscular pulmonary arteries."

Shapiro,[102] in 1966, undertook an investigation to determine the effects of acid-base changes upon PVR. Data was obtained by means of cardiac catherization of anesthetized dogs. He reported an increase of PVR during metabolic acidosis and a decrease of PVR during metabolic alkalosis, but no change in PAP during either experiment. In experiments in which pH was held constant by means of varying ventilation, the infusion of acid or base produced no consistent change in PVR, leading Shapiro to conclude that PVR is pH dependent. Changes in cardiac index did occur during the experiments which was sufficient to explain, in part, the changes in PVR. Furthermore, Shapiro was unable to conclude "...whether the change in PVR due to changes in pH results from pulmonary vasomotion or result from secondary passive effects of changes in LAP."[102] Shapiro found a statistically significant correlation of pH and PVR.

Bergofsky [10, 9] in a study performed on subjects with a normal pulmonary vasculature was unable to find any effects of increased pH upon hypoxic

pressor responses. However, Vogel[113] had an interesting clinical opportunity to study a patient with no pulmonary disease who presented with obesity and hypoventilation. The regulating importance of arterial P_{O_2} and (H+) upon the pulmonary arterial pressure was studied using catherization data. In this patient, hyperventilation with a consequent increase in P_{O_2} resulted in a decrease in mean PAP. Using THAM, the pH was then increased with no change in P_{O_2}, but a similar fall in PAP occurred. In this same patient, changing the inspired air to 100% O_2 and thus raising P_{O_2} with no change in pH led to a slight increase in mean PAP. Therefore, Vogel concluded that in this patient with normal lungs and chronic hypoxia, (H+) had a significant role in regulation of PAP. Whereas Enson[42] had previously suggested that an increase in the pH would alter the pulmonary pressor response to hypoxia only in patients with chronic pulmonary disease, the studies of Vogel extend this mollifying effect to a normal vasculature. Vogel was unable to find evidence of increased release of lactic acid in this patient which is interesting in the light of Liljestrand's[68] suggestion that local acid release mediates the pulmonary response to hypoxia.

In another perfusion experiment using isolated dog lungs, Lloyd[71] studied the influence of pH on the pulmonary vasoconstrictor response to hypoxia. Without exception he demonstrated a pressor response to hypoxia and was then able to reduce the magnitude of this response by increasing the pH. These studies were in agreement with those of Enson[42] in which an increase in pH diminished the pressor response to hypoxia in patients with chronic lung disease. Lloyd suggested that local pH might be influential in the hypoxia pressor mechanism.

In summary, many investigators have studied the effects of acute hypoxia upon the pulmonary vasculature. An increase in PVR with acute hypoxia was reported by Lewis,[67] Nahas,[85] Stroud,[107] Cropp,[28] Berry,[12] Lloyd,[72] Kentera,[63] Bergofsky,[11] and Wilcox,[115] to list but a few. Nevertheless, other workers have reported no change or a decrease in PVR with hypoxia.[65, 116] This controversial topic also includes those who adhere to both points of view, notable Sackner[100] and Aviado.[5]

The site of the vasomotion and the means by which it is mediated is a subject of even greater controversy. Several investigators have demonstrated that diffusion of O_2 can occur into the precapillary vessels,[59, 32, 15] and such data would support the concept that vasomotion was a precapillary phenomenon. Enson[42] emphasizes that these vessels' walls are indeed accessible to local (H+) and oxygen changes and theorizes that it may be these environmental changes which lead to vasomotion and redistribution of blood flow according to ventilation.

In man, hypoxia has been found to result in an increased PAP (Motley,[82] Westcott,[114] Doyle[37]) with no effect upon pulmonary wedge pressure (Westcott,[114], Doyle[37]). On the basis of these observations, it has been suggested that hypoxia results in constriction of muscular branches of the pulmonary artery. Bergofsky provided evidence that hypoxia confined to precapillary segments could produce pulmonary vasoconstriction.[11] The study by Morkin[81] supports the point of view that the precapillary vessels may be involved in vasomotion associated with hypoxia, in that he describes an increased PAP with no change or a decrease in flow pulse in the pulmonary capillaries. There was no associated increase in PA wedge or LAP and so Morkin concludes that it would not be reasonable to implicate either post

capillary vessels or the pulmonary veno-atrial junction as being involved in vasomotion.

Rivera-Estrado[96] found an increase in pulmonary wedge pressure with no change in LAP during acute hypoxia. Such data support the thesis of a post capillary change in resistance, but this particular study did not include measurements of cardiac output.

Berry,[12] however, agrees with Rivera-Estrado and found an increase in post capillary, but not precapillary resistance. McLaughlin[78] reported finding an increase in PVR with hypoxia that was due to a rise in post capillary resistance, and presented evidence to indicate that this response was mediated by the sympathetic nervous system. Nissel[88] demonstrated pooling of blood in the lung with a coincident increase in PAP subsequent to stimulation with hypoxic gas mixtures, and concluded that the vasoconstriction occurred on the venous side of the capillary bed. Sackner[100] is in the middle of the road, and states that his studies "indicate that significant vasomotor activity is present throughout the pulmonary arterial tree." Fishman,[46] in a recent review of the literature, was led to conclude that the largest body of evidence suggests that the active segment is the post capillary portion of the pulmonary vasculature.

The studies of Liljestrand[68] and Motley[82] were, in a large part, responsible for the suggestion that local hypoxia might be the stimulus for local changes in resistance and consequent shunting of blood. In response to this, many investigators attempted to demonstrate a differential in perfusion in various lobules or lobes according to their exposure to different gas mixtures. Fishman[46] points out that most

investigators have been unable to demonstrate a redistribution of blood from a hypoxic lung to a well aerated one, until the hypoxia was severe enough to correspond to the oxygen tension of venous blood (5%). Desfares,[34] in 1960, was able to demonstrate redistribution of blood using hypoxia caused by 10% oxygen. Dirksen[35] showed a shift of blood flow during unilateral hypoxia in rabbits while Atwell[4] and Peters[91] showed a similar effect in dogs.

Moore and Cochran[79] had attempted such a study and were unable to demonstrate a redistribution of blood flow through a dog's lung. Jacobeaus[58] found no redistribution of flow in man. The variability of the results included Dirksen[35] and Heemstra's work in which there was a relative increase in blood flow occurring in the rabbit lung. However, this effect required hours to occur and was certainly subject to doubt. Rahn,[93] however, was able to demonstrate a redistribution that occurred in a matter of minutes in a dog preparation. Atwell[4] ventilated one lung in a dog preparation with air that had been equilibrated with pulmonary arterial blood and noted a relative shift of flow to the lung ventilated with room air (approximately 21% oxygen). Of note is the fact that pulmonary venous pressure was not elevated when the one lung received the hypoxic air mixture. This study was far from definitive, however, in that only one half of the small number of animals used showed the hypoxic pressor response. Also, inherent in this study, was a relative hypercapnia associated with the hypoxemia (decreased arterial saturation) and several investigators have claimed a pulmonary pressor response for hypercapnia.[43, 87, 38]

Using unilateral nitrogen breathing in dogs, Peters [91] demonstrated a reduction in blood flow to the hypoxic lung with a calculated increase in vascular resistance. Peters[91] believed that this provided evidence to refute the hypothesis of Liljestrand[68] that the pressor response was due to a low mixed venous oxygen saturation for in these experiments both lungs were perfused with blood of the same oxygen content.

Lopez-Majana[74] in 1966, reported an interesting study using radio-isotopes in men with pulmonary disease to assess the effects of regional hypoxia upon the distribution of pulmonary blood flow. In these studies scans were obtained using I^{131} serum albumin and were interpreted as showing a partition of the blood flow. In sedated subjects when one lung was ventilated via the tracheal cannula with 100% nitrogen, a resulting 42% decrease in flow was found on the hypoxic side, with a coincident increase in ventilation to that side. Such data provides convincing evidence that as Lopez states, "the lung is capable of altering regional perfusion and ventilation in a manner ideally suited to minimize change in alveolar and pulmonary capillary oxygen tensions." Arborelius,[2] in a study performed on humans with normal lungs, found that flow to a hypoxic lung reached a minimum within five minutes. Ventilation increased significantly after approximately fifteen minutes. Arborelius interprets these findings as in accord with those of Desfares[34] and concludes that the results support the theory of Von Euler[43] and Liljestrand (1946) that the oxygen tension in alveolar gas acts as a physiologic stimulus for keeping a normal balance of ventilation and flow within the lungs.

Staub,[106] in 1963, attempted to use histologic, rather than physiologic means of demonstrating the site of the action of hypoxia on the

pulmonary vasculature. Using a rapid freezing technique, he demonstrated a smaller internal diameter of pulmonary arteries in hypoxic lungs compared to their control counterparts, in a separate ventilation experiment. Staub concluded that the arterial portion of the circuit was the site of an active constrictive process and hypothesized, as had others, that the "functional value of an increase in pulmonary vascular resistance due to hypoxia is the local adjustment of perfusion to ventilation of the terminal respiratory units."

In a subsequent study Kato and Staub[61] selectively ventilated one lobe of a cat's lung with either hypoxic or hypercapnic gas mixtures while all other lobes received oxygen. Measurements of internal diameters of small muscular pulmonary arteries after rapid freezing revealed that in the presence of regional alveolar hypoxia without systemic hypoxemia, there was actual vasoconstriction of these muscular segments. This data correlated well with the large calculated decrease in blood flow to the hypoxic segment. While such data add evidence to the belief that the precapillary region of the pulmonary vasculature is the active vasomotor site, they also demonstrate the partition of perfusion from hypoxic to well ventilated regions of the lung.

While such a body of evidence, though controversial, has been compiled, other investigators have pursued the question of whether the pressor response is a local or central reflex, and how it is mediated. Accordingly, the literature contains a wealth of studies ranging from the anatomic to the biochemical. Representative and pertinent studies will be presented below.

Verity[110] performed a histologic study of the innervation of the pulmonary artery of the cat from the valve ring to the lobar bifurcations. Fibers from both sides to the main pulmonary bifurcation consist of elements derived from the vagus, recurrent laryngeal, and branches from the stellate ganglia. He describes a diffuse plexus of both myelinated and non-myelinated fibers which permeate the adventitia and there travel with vasa vasora into the media. The fibers in the media were found to be mainly efferents and a contractile response (in vitro) was elicited by electrical stimulation near the stellate ganglia, but not by stimulation of the vagua. Blocking with hexamethonium was noted to reduce, but not eliminate, the response to electrical stimulation. Of note, Verity did not find the classical pressor-receptors in the cat PA, but found simple fiber arborization throughout the vessel wall.

Fisher,[44] using data obtained in an anatomic study, describes a specie variation in the innervation of the extra- and intra-pulmonic vessels. He notes that in the cat, the intra-pulmonic arteries have but a sparce network of fibers contrasted to the veins which appear richly innervated. Such data provide strength for those who believe the venous phase is the prime site of vasomotion; but, this anatomic data does not substantially weaken the thesis that, physiologically, this vasomotion may be most significant in the arterioles.

Several investigators have provided evidence that pressor receptor-like endings exist in the pulmonary artery of the cat[17, 109] and dog.[24] verity and Bevan[111] in 1965, presented a morphologic study which provides evidence for an afferent fiber system in the adventitia of the pulmonary artery. Some of the fiber endings consisted of fine unspecialized arborizations, but many had the characteristics of de Castro Type II presso-receptor endings. That such pressoreceptors may be involved in a reflex

ventilatory change was proposed by Bevan and Kennison.[14] They describe a ventilation-regulating reflex similar to a Bejold-like reflex, that originates from "a pressure sensitive zone in the region of the PA bifurcation." This is of interest in that it supports the thesis that changes in pulmonary artery pressure are reflexly capable of inducing respiratory and perhaps systemic effects.

Coleridge[24] reported an interesting study in which dogs anesthetized with chloralose were used to demonstrate a relationship of PAP to impulse activity in fibers from pulmonary artery baroreceptors. He reports an increased frequency of impulses with a rise in PAP and went on to characterize the baroreceptors further by finding that the activity noted was, in general, confined to systole, and that pulsatile pressure was a more effective stimulus than constant pressure. Coleridge,[25] in a different study, describes recordings from pulmonary baroreceptors via fibers dissected from the cervical vagus. Histologic studies of these preparations were used to identify the sensory endings which he describes as being fine branched coiled fibers that were in, or in contact with, the media of the right or left PA but not the main PA. This work was not done on cats, however.

Osorio[90] described a reflex change in pulmonary and systemic pressures in response to stimulation of pulmonary artery baroreceptors. Osorio inflated a balloon in the pulmonary artery and noted both a rise in systemic and pulmonary artery pressures unaffected by vagotomy. He concluded that the increase in PAP was of reflex origin from baroreceptors in the larger branches of the pulmonary artery, thus a pulmo-pulmonary reflex. Kinnisin,[64] in a study of reflex mechanoreceptors, reported a

reflex by which a decrease in PAP, with no change in aortic or right atrial pressures or heart rate, resulted in an increase in respiratory rate and depth.

Such studies have many implications. Each is a significant contribution toward the understanding of a certain reflex mechanism whether intrinsic or extrinsic to the lung. While these reflexes do not directly concern the hypoxemia or acidemia pressor response they do show that reflex mechanisms may exist in the pulmonary vasculature. Many different preparations have been used to demonstrate that the musculature of the pulmonary arteries is responsive to electrical or chemical stimuli. Smith,[104] in 1951, undertook an "in vitro" study of the effects of anoxia upon isolated strips of pulmonary vessels obtained in the post mortem period. In these studies, vessels which contricted in response to epinephrine did not constrict with hypoxia. However, as he emphasizes, the pulmonary vessels studied in these experiments were generally large, and it may well be that it is smaller vessels which are most active in the vasomotion in response to hypoxia. Bergofsky[8] showed that isolated strips of pulmonary artery in an "in vitro" preparation respond to hypoxia by constricting. Such data provides support for the theory that the response is a local phenomenon.

Somlyo[105] demonstrated in an "in vitro" preparation of canine main PA that isotonic contractions can occur in response to various stimuli including catecholamines and serotonin. While this does indicate that it is feasible for active regulation of the pulmonary artery diameter by its' inherent smooth muscle, the characteristics of the more distant (and probably significant branches of the artery) were not elucidated by this study.

An increase in pulmonary artery muscle mass subsequent to chronic hypoxia has initiated the controversial subject of, "is the new muscle the cause or the effect of the hypoxia?" While this is still debated, Naeye[83] used a chronic unilateral hypoxia preparation to demonstrate an increase in muscle mass. However, this occurred in both arteries and veins and several factors, such as pulmonary pressure, were presumptive, rather than factual. While such data is most useful in the study of the etiology of pulmonary hypertension and its relation to the pulmonary vessels, it also serves to demonstrate that the muscle mass is responsive. Whether the stimulus be physical or chemical remains unsolved. The data is further useful in support of the concept that the vasculature responds directly to changes in its biochemical environment and I refer to the previously cited studies that demonstrate the diffusion of alveolar gases into the pre-capillary pulmonary arterioles.

A variety of physiologic studies have demonstrated reflex control of the pulmonary vasculature. Daly[30] found evidence in anesthetized dogs that pulmonary vascular resistance could in part be controlled by extrinsic vasomotor nerves. Daly[31] also claimed a decrease in pulmonary vascular resistance elicited by stimulation of carotid body chemoreceptors. Viswanathan[112] presented evidence that reflex vasoconstriction does occur with the accidental finding that the inflation of a balloon catheter during pulmonary angiography results in an increase in pulmonary artery pressure. Viswanathan concluded that "the rise in pressure in these cases is due to reflex vasoconstriction of pulmonary arterioles as a whole" and considered these findings as "direct evidence that even a small pulmonary embolus can produce reflex vasoconstriction and consequent increase in pulmonary vascular resistance."

Agrest,[1] stimulated by the controversy of whether or not the nervous system played a role in the control of the pulmonary vascular bed, undertook an investigation of the effects of bladder distention as an autonomic stimulus upon the pulmonary circuit. These studies, unique for many reasons, involved right heart cardiac catherization in paraplegics in whom bladder distention evidently produces prominent autonomic reactions. Data revealed an increase in pulmonary vascular resistance greater than the coincident increase in systemic resistance and a PAP increase of 50-75%, without a change in cardiac output. This led Agrest to conclude that it "offers a good argument in favor of this nervous control" of the pulmonary vasculature.

The presence or absence of vasomotor control of the pulmonary circulation continues to be a subject of controversy. Comroe[21] stated that the pulmonary circulation "is not lacking in vasomotor regulation although this appears to be excited by stimuli different from those in the systemic circuit." Wood[118] believes in a vasoconstrictive factor in pulmonary hypertension.

Several investigators have claimed that epinephrine can cause vasomotion in the isolated perfused cat lung preparation.[19, 48] Others have demonstrated an increase in PAP[43] or an increase in PVR[41] in response to epinephrine in anesthetized animals. In experiments using a constant infusion of epinephrine, Duke[40] was unable to demonstrate any change in PVR in an anesthetized cat preparation. However, the same infusion after stellatectomy resulted in an increased PVR that was reversible. Stellatectomy alone resulted in a decrease in cardiac output. Duke was

led to conclude that there may be a constant sympathetic tone to the pulmonary vessels, which when this influence is removed, respond to epinephrine.

Rose[98] presented evidence that norepinephrine had a direct vasoconstrictive effect on the pulmonary vasculature effecting an increase in PAP with a concomitant decrease in flow. However, Aramendia[3] reported no change in PAP and only slight changes in PVR subsequent to infusion of norepinephrine and/or isoproterenol. The changes in PVR can probably be attributed to the changes in cardiac output that occurred concomitantly.

McGaff,[77] stimulated by the use of ganlionic blockade in the treatment of pulmonary edema, undertook a study to determine if such drugs had a direct vasodilatory effect on the pulmonary vasculature. Using arfonad, he produced a decrease in PAP, LAP, PA wedge pressure, as well as cardiac output, but there was no significant increase in pulmonary blood volume to suggest vasodilation, as opposed to mere relaxation of vessel wall with decreased intra-luminal pressure. Looking at this data from another point of view, it provides some evidence that there is no set sympathetic "tone" which maintains pulmonary vascular dynamics.

Duke,[39] using an isolated perfusion technique, reported an increase in sympathetic activity as well as an increase in rate and depth of inspiration in response to anoxia of the pulmonary artery perfusate. Nahas[84] found the pulmonary vasculature of sympathectomized dogs to be less responsive to hypoxia than that of normal dogs and supported the concept of an autonomic mediation for the vasopressor response.

Lloyd,[70] in 1964, had concluded that the vasoconstriction seen in response to pulmonary hypoxia was an "intra pulmonary reflex rather than a direct alteration of vascular muscle tone due to oxygen deprivation."

In subsequent experiments, electrical stimulation was noted to cause a reversible increase of PAP that was not blocked by atropine, but was blocked by dibenzilene or reserpine. However, the increased PAP caused by hypoxia was not changed by dibenzilene or reserpine. Also, of importance, was the finding that an increase in pH abolished the response to hypoxia, but not to electrical stimulation. While Lloyd uses these data to propose an intrapulmonary reflex, it also provides support for the view that the sympathetics are not the mediators of the response and that there is an interaction of pH and P_{O_2} in their effect upon the pulmonary circuit.

Bergofsky[11] provided evidence that hypoxemia of the brain and carotid chemoreceptors resulted in no change in PAP, or PVR, while the same animal still responded to hypoxia. If these animals were indeed reflexive, this supports the theory that the response is on the basis of a local effect or reflex due to the hypoxia. Similarly, Renais[94] perfused the dog brain with intermittent hypoxia and found no change in PAP in animals that showed a pressor response to alveolar hypoxia. Fritts[47] found that the response was also unaffected by a local division of the pulmonary nerve plexus. Judson[60] on the other hand, has reported that sympathectomy or local sympathetic block prevents the pressor response to hypoxia.

Maxwell [76] has shown that guanethidine produces a selective blockade of the post-ganglionic sympathetic pathways. In a study using apparently normal subjects upon whom cardiac catherization was performed, guanethidine was not found to cause any changes in the pulmonary vasculature. Hypoxia, as an isolated stimulus, did result in an increased PAP and CO with no change in wedge pressure. With guanethidine, there was no change in the person's response to hypoxia, and thus Harris[54] concluded that "it seems

improbable that the sympathetic nervous system plays a part in the effects of hypoxia on heart and pulmonary circulation." That the pulmonary pressor response may occur without the autonomic nervous system or neurohumor is supported by many investigators. Such evidence has, in part, led Fishman[46] to conclude that pulmonary vasomotion is a consequence of local effects on the pulmonary vessels and at present the greatest amount of evidence suggests that the active segment is in the post capillary portion of the pulmonary vasculature.

VI. DISCUSSION

The pulmonary vasculature is unique not only in design but also in function. It is unlike the system of vessels to other body organs which serve as conduits of nutrition. Instead, its primary role is its function in external respiration, with secondary functions as a blood resevoir, a filter, etc. Cournand[26] compiled experimental data obtained in observations on man and animals and presented some characteristics that in part define the pulmonary circulation. These characteristics are: a) an equal amount of blood flows through the pulmonary and systemic circulations; b) the pulmonary vasculature is a low pressure system while handling the same flow as the corresponding high pressure systemic circuit. This is dependent upon the distensibility of the pulmonary vessels and the large capacity of the vascular bed. The essential difference is thus the low vascular resistance; c) the distribution of blood through individual regions of the lungs depends on local conditions rather than nervous system control. Cournand inferred, on indirect evidence, that the mechanical factor of change in resistance provided for shunting of blood on a local level. Subsequent observations provided Cournand and others with evidence that active vasomotion might indeed serve in the regulation of pulmonary pressure and flow. However, the mechanical model is still valuable.

Indeed the pulmonary circuit is a low pressure system in which counterparts of the systemic arteriole,[45] a resistance vessel with a high ratio of wall thickness to lumen do not exist. The large pulmonary vessels, unlike systemic vessels, rapidly divide into thin walled, large lumened channels. The media of the main pulmonary artery is but half the thickness

of that of the aorta,[45] and, similarly, the small pulmonary arteries have far less smooth muscle than do their systemic counterparts. Few would doubt the proposition that vascular smooth muscle is a prerequisite for vasomotion, and it is logical to assume that vessels that are more heavily endowed with muscle are more likely to constrict and less likely to be passively dilated. While the small muscular arteries in the systemic circuit are the site of vascular resistance, one would not expect the corresponding pulmonary arteries with their scant musculature to serve as resistance vessels. The pulmonary pre-capillary vessels,[45] however, 100-1000 u in diameter have a well organized media and histologically would appear to be better suited for vasomotion. No smooth muscle or other types of contractile elements are believed to exist in the pulmonary capillaries and the venules have but a scant amount of smooth muscle in their walls. Whereas the pulmonary veins have but a small quantity of irregularly placed smooth muscle and from a histologic point of view would not be expected to be a major source of vasoconstriction, the region of the veins where they enter the left atrium is surrounded by a sleeve-like extension of myocardium which conceivably could serve as "throttles" to flow.[45]

Cournand,[27] in 1947, obtained pressure tracings from the left atrium in patients with atrial septal defects and demonstrated that the LAP exceeds the mean RAP, and that the cyclical range of pressures were also greater on the left than the right. He concluded that the left atrium and the pulmonary venous system, as a resevoir, were less distensible than the corresponding system on the right. Opdyke,[89] Little, and others

confirmed this data in experiments performed on dogs, and such evidence lends credence to the view that slight distention of a normal left atrium may be accompanied by considerable pressure changes in the venous resevoir. From a mechnical point of view, therefore, it is easy to conceive of an effect on the pulmonary artery pressure resulting from such passive changes.

The pulmonary blood flow in the normal vasculature is equal to the cardiac output of the right side of the heart. The first measurements of pulmonary arterial pressure were reportedly made by Beautner in 1852.[13] In general, the contour of the pressure wave is similar to that of the aorta, the major difference being amplitude.[45] Fishman[45] discusses the use of pressure-flow curves as a measure of pulmonary vascular resistance and makes the point that the physical laws that have been derived to explain the relationship of pressure, flow and resistance cannot be applied precisely to a vascular bed, for the vasculature is a "non-linear, frequency dependent system perfused by a complex fluid" in which flow is pulsatile. Therefore resistance is not a constant charcteristic of a particular vessel or group of vessels, but rather varies with the physiologic circumstances.[45] Since the pulmonary circuit is a low pressure circuit and yet is perfused with the same amount of flow as the systemic circuit, the pulmonary resistance must be proportionately less than the systemic. Fishman[45] discusses possible errors in the calculations of pulmonary vascular resistance and lists a number of factors aside from vasomotion which could cause a change in vascular resistance (Table 6).[45]

The knowledge of the above factors has caused some degree of dissatisfaction with the use of calculated resistance, and it is for this reason

that pressure-flow curves are advocated by Fishman[45] and were used in this study to demonstrate graphically the relationship of flow versus pressure during control and experimental conditions. A study of pulmonary vascular compliance was undertaken to determine the passive pressure-flow relationship, knowledge of which is essential to an investigation of vasomotion. These studies also demonstrated that the vasculature, as studied in this experimental preparation, had the same compliance characteristics already shown by Sarnoff[101] to be typical of the pulmonary vasculature. Sarnoff demonstrated in an isolated lung perfusion that for "a given volume of blood in the system, the pressure is higher while volume is increasing than decreasing." Thus, the shape of the compliance curve differed during the periods of infusion and withdrawal, a phenomenon which was attributed to stress relaxation of the vasculature,[101] and reflects a change in distensibility.

In the experimental preparation used in the investigation of acidemia and hypoxemia, compliance studies were performed by means of transfusion and hemorrhage of whole blood. Pulmonary pressure-flow curves were obtained and a representative example is shown in Figure 23. In this study, for a given flow the pulmonary pressure was found to be higher during transfusion than during hemorrhage, and thus, the compliance curves were different during periods of infusion and withdrawal. These data are in agreement with the work of Sarnoff and the compliance curves are of similar shape. Figure 23A also shows the same compliance study obtained during a period of acidosis. Figure 23B represents a similar study performed on a different animal in which two degrees of acidemia were studied. These preliminary data demonstrate a shift of

the entire compliance curve (a pressure-flow curve) to the left during conditions of acidemia as compared to the control. Also of interest, the data reveal that there is a more pronounced shift of the compliance curve with a greater magnitude of acidemia. The left atrial pressures did not change significantly during performance of the compliance curves, either during control or experimental conditions. Therefore, the changes noted in no way reflect the effects of passive influences of the left atrial pressure, but rather characterize the distensibility of the pulmonary vasculature. Such preliminary findings suggest that the pulmonary vasculature might indeed be responsive to stimuli such as acidemia and that the use of the experimental preparations previously described would appear to be justified.

In these experiments systemic arterial hypoxia resulted in a rise in pulmonary arterial pressure, and pulmonary vascular resistance at any given cardiac output. One of the prime advantages of the experimental design was the availability of data with which pressure-flow curves could be formulated and compared. Previous experiments have varied considerably in design in order to measure pressure and flow, either in anesthetized, non-anesthetized or isolated preparations. To my knowledge, however, there is no account in the literature of a preparation allowing control of cardiac output. Whereas cardiac output or pulmonary flow has been measured in a variety of ways, including the Fick principle, dye dilution and electromagnetic flow probe, the effect of the changes in cardiac output encountered during an experiment has never been quantitatively analyzed. In my experiments it was entirely possible to control the cardiac output by means of altering the venous return to the right side

of the heart. Changes in cardiac output, and therefore changes in pulmonary flow were readily achieved and the PAP, PA-LA and PVR could be determined for a given flow during control and experimental conditions. Much controversy has filled the literature regarding errors in the techniques of measuring cardiac output, to the effect that in some experiments two methods were used, both yielding different results and and therefore opposite conclusions. An example of such data was the work of Nahas[85] in which the effect of hypoxia was studied using non-narcotized dogs. In these experiments Nahas reports an increase in PAP and PVR with a decrease in cardiac output during conditions of hypoxia. One would be led to conclude that the increase in PVR was a result of the hypoxia. However, simultaneous measurements of cardiac output by means of the dye dilution technique revealed an increase in cardiac output, and Nahas concluded that the increase in flow might well account for the increase in PAP, with no actual change in PVR. Liljestrands'[68] original observation of the increased PAP with hypoxia have been subject to question because cardiac output was not measured.

Cournand,[26] in a recent review, discusses the use of the Fick principle as a method of determining pulmonary flow. Since this method was developed, a variety of indirect means of determining flow have been devised including the use of isotope tracers, thermal and sonic flow meters, electromagnetic flow meters, and rotameters. Moran,[80] in a recent review, discusses the properties of the ideal flow meter which, to date, can be approached, but has yet to be developed. Both the rotameter and the electromagnetic flow meter[80] can generally be calibrated to within a 5%

error, a figure which is less troublesome when it is realized that it is a constant except at the extremes of flow. In the experiments reported herein, both systems were repeatedly calibrated in the manner suggested by Moran, and over a three year period only a minute variation was encountered.

The flow meters were used to determine the cardiac output in ml/min of the left side of the heart; a flow level which, plus the coronary flow, is equal to the pulmonary flow. While such a method is an indirect measurement of pulmonary flow it was chosen for several reasons.

First, throughout the range of flow achieved, left cardiac output plus coronary flow is equal to right cardiac output, with the exception of the brief intervals necessary for equilibration after a sudden change in venous return.[50] Since a considerable period was allowed for equilibrium after each increment of venous return, this potential source of error was avoided.

Second, the method of application of the electromagnetic flow probe is of great importance in the recording of pulsatile flow.[80] In the preparation using adult cats the length of the main pulmonary artery was found to be slightly too short for correct application of the flow probe. Under these circumstances when improperly placed, the probe compromised either the coronary arteries or the right pulmonary artery.

There remains one factor which must be considered when aortic flow is used as an indication of pulmonary flow. If there is a vessel proximal to the point at which flow is being measured, then the true cardiac output is greater than the measured amount of flow. In these preparations, the only vessels that were patent and proximal to the measuring

device (either electromagnetic probe or the Shipley-Wilson Rotameter) were the coronary arteries. If coronary blood flow is relatively constant, i.e., 4-5%[50] of the average 300 ml cardiac output, then pulmonary flow would be 4-5% higher than that measured in the aorta, a difference of 12-15 ml/min. This factor would not be a source of error for it would be constantly present. That is to say, the pulmonary flow for a particular pressure would be slightly higher than recorded during control and experimental conditions.

In these experiments, the effects of hypoxemia were studied and showed an increase in the pressure for a particular flow. Hypoxemia has been reported by Love and others[75] to cause a decrease in coronary vascular resistance with a concomitant increase in flow. If this occurred in the present experiments, then the cardiac output measured would be less than the actual right heart output by more than 5%. The difference x%-5% would represent an unmeasured increment in pulmonary flow during hypoxia. If the magnitude of this increment were large, then the change in PA pressure might, in part, be a passive phenomenon. This is unlikely for the following reasons:

1) Since coronary flow is in part a function of cardiac work[6], changes in systemic arterial pressure and left cardiac output would be expected to change flow. However, systemic pressure was held constant during the entire experiment.

2) The increase in coronary flow during systemic hypoxia has ranged in various investigations between 50 and 100%[52] of the original flow. Extrapolating this data reveals that the actual increase would be 7.5 ml to 15 ml. Lategola[66] was able to draw a passive pressure flow curve for

the pulmonary vascular bed of an intact dog. In these experiments he plotted ΔFlow (%) on the abscissa against ΔP (%) pressure on the ordinate and found a curve with a gradual slope until approximately 250% flow when the slope of the curve increased abruptly. Therefore, over the range of flow encountered in my experiments (approximately 100-200%) a great variation in flow exerts passively only a slight change in pulmonary pressure.

Taking such data one step further, one finds in my compliance data, that it required an average change of approximately 50 ml flow for an increase in pulmonary pressure of 1 mm Hg. It is therefore apparent that if the coronary flow increases 100% thus adding 15 ml to the pulmonary flow, the passive effects of such a change would be an approximate elevation of PA pressure by 0.3 mm Hg. In the hypoxemia experiments, the mean ΔPA was calculated to be 3.4 mm Hg and 5.8 mm Hg in the acidemia experiments. Thus, the contribution of a passive change would be a maximum of 9% and 5% respectively to the overall change in pulmonary pressure. It has long been believed that sympathetic stimulation may increase coronary flow via its effects on systemic resistance and work.[50] Since the arterial pressure was constant, there is no reason to expect a passive increase in coronary flow due to sympathetic stimulation in these experiments. Hackel[52] has shown in experiments on adrenalectanized-sympathectanized dogs that the sympathetic nervous system is not involved in the response of coronary flow to hypoxia.

In the experiments studying sympathetic stimulation, it was elected to use the Shipley-Wilson Rotameter for measurements of cardiac output. This was done to avoid dissection about the root of the great vessels

with possible damage to autonomic nerve fibers which would be necessary for proper placement of an electromagnetic flow probe.

The methodology used in the study of the effects of sympathetic stimulation upon the pulmonary vasculature was derived in part from the classic experiments of Harvey Cushing, who elucidate the "CNS ischemic reflex." In experiments performed in 1901, Cushing[29] described a servo-like mechanism by which auto-regulation of CNS perfusion occurred. When CSF pressure was elevated to exceed arterial pressure (thus cerebral compression), the animal's systemic blood pressure reflexly increased to exceed CSF pressure, and thus afforded perfusion. In the course of his experiments, Cushing describes the rise in CSF pressure as resulting in evacuation of bowel, bladder, pronounced slowing of the heart as well as prompt rise in blood pressure; all such effects known to be mediated via the autonomic nervous system. Cushing proceded to demonstrate the neural efferents of this reflex by selectively cutting the vagi and narcotizing the spinal cord. In concluding that an "increase in intracranial tension occasions a rise in blood pressure which tends to find a level slightly above that of the pressure exerted against the medulla", Cushing aptly described what is now known as the CNS ischemic reflex.

Of importance is the fact that Cushing[29] produced cerebral compression and thus effected CNS ischemia locally, rather than by proximal ligation of the feeding arteries with resultant stimulation of carotid and aortic receptors. Guyton[51] selectively denervated these structures as he produced a proximal type of ischemia and his data reveal a contribution to the ischemic pressor response by reflexes originating from the carotid sinus.

In essence Guyton's results were identical to Cushing's and he agrees with the latter's conclusion that there is a pressor response to CNS ischemia. Guyton further states that this reflex is "probably mediated through the sympathetic nervous system" to which Cushing's data would add credence.

Further evidence that this mediation was indeed via the sympathetics was provided by Grimson[49] in 1937. He showed a decline in systemic blood pressure after sympathectomy in dogs which gradually returned to normal over a period of six months. He confirmed that a rise in CSF pressure elicited a rise in blood pressure in normal dogs and went on to demonstrate that such an increase in CSF pressure after sympathectomy resulted in a decline in blood pressure and ensuing death. These experiments, as did Cushing's, revealed the presence of a parasympathetic outflow, along with the sympathetic component, which was reflected in a marked bradycardia and which was negated by vagotomy.

In my experiments, CNS ischemia was produced proximally by shunting of blood from the brachiocephalic vascular bed to a venous return line, and thus effecting an autonomic discharge without inherent changes in vascular dynamics. Both parasympathetic and sympathetic outflows were encountered as was expected and a selective chemical blockade was employed to differentiate the responses.

This investigation demonstrates that the pulmonary vasculature responds with an increase in mean pulmonary artery pressure, perfusion pressure and resistance to both the stimuli of systemic acidemia and hypoxemia. Furthermore, the response to the combination of these two stimuli is greater than the response to either stimulus alone.

It has also been shown that mean pulmonary pressure and perfusion pressure do not increase in response to strong sympathetic stimulation, although pulmonary systolic pressure may increase.

The results of this study are in basic agreement with those of Liljestrand,[68] Motley,[82] Enson,[42] Rudolph,[99] and others, in that they support the thesis that hypoxemia and/or acidemia cause a pulmonary pressor-response with a resulting increase in PAP and PVR. That the stimuli are interacting was reflected in the fact that the combination of acidemia and hypoxemia resulted in a far greater response than either stimulus alone. This is in complete agreement with the work of both Enson and Rudolph.

Teleologically, one can assume that such a reflex plays a role in the regulation of local perfusion according to ventilation. Furthermore, the studies of Coleridge and others[24] which describe a "pulmo-pulmonary" reflex may in part describe a means for the active regulation of ventilation according to perfusion and perfusion pressure, thus completing a teleologic circuit.

These experiments amply verified that a pressoresponse occurs and that it is an active rather than a passive phenomenon. The site of the vasomotor response, however, has not been elucidated by this work. Pulmonary vein or wedge pressures were not monitored. At the same time, this study does not refute the predominant belief that the active segments of the pulmonary vasculature are the post-capillary vessels. It does present strong evidence that the response is not mediated via the sympathetic portion of the autonomic nervous system, however. Furthermore, it supports the tenet that the response is either a local direct effect,

or is reflexly mediated within the lung.

Of the many influences that could theoretically influence pulmonary vascular dynamics, respiratory mechanics and LAP are probably the most influential. Rodbard emphasized the concept that cyclical changes in airway pressures could be reflected in PVR via extraluminal pressure applied to capillaries, and might be responsible for some redistribution of blood flow to various lung regions. Bannister[7] found that perfusion pressure was directly related to inflation pressure (P_i) when P_i was greater than LAP. Permutt and Riley[95] also demonstrated that variation in LAP had no effect on pulmonary flow if P_i exceeded LAP (the "waterfall" concept).

Such data would mean that the venous portion of the perfusion pressure is determined by P_i when P_i exceeds LAP. Therefore since P_i can be considered as being applied to the alveolar-capillary bed, it can be seen that flow can be altered by P_i and, therefore, P_i must be considered in evaluating PVR. DeBono[33] found a linear relationship of alveolar pressure and PAP, both during inspiration and expiration. De Bono comments that the alteration in PVR (calculated according to PA-LA/Flow) during inspiration is actually artifactual for the "downstream end of the gradient has shifted from the LA to the alveoli." The experimental evidence showing a decrease in PVR with a rise in LAP[16, 20, 53] is probably in error due to the use of the wrong gradient in the calculations.[33]

Colebatch[23] reported an increase in resistance to lung inflation due to vagal stimulation, and attributed the effect to bronchoconstriction. The coincident small increase in PVR was interpreted, and probably justifiably, as due to the decrease in cardiac output. This finding was

similar to Lloyd's[73] in which he reported an increase in inflation pressure subsequent to electrical stimulation via arterial and bronchial cannulae that was abolished by atropine.

It is apparent, therefore, that airway pressure needs to be considered. It is to be noted that all pressure-flow measurements in this investigation were obtained under stable conditions after passive deflation of the animal's lungs for brief intervals. Thus, the results herein reprted cannot be attributed to the passive influence of bronchoconstriction or positive pressure inspiration. LAP was monitored and LAP-Flow curves were also obtained. Such data reveal no shift of these curves and significant stability of these pressures to make negligible any contribution, in a passive manner, of LAP to PAP.

It is concluded from this study that the pulmonary circulation is by no means a passive vehicle for flow. On the contrary, this investigation supports the suggestion that there is a significant active vasomotor response to acidemia and hypoxemia, singly or in combination. This study also rejects the theory that passive influences of airway or left atrial pressure are necessary for the above responses. While an attempt was not made to elucidate the site of vasomotion in the pulmonary vasculature, evidence is presented to refute the concept that the sympathetic portion of the autonomic nervous system is the mediator for this response.

VII. SUMMARY

The controversial issue regarding the existence of an active pulmonary vasomotor response to hypoxemia and acidemia is presented. The pertinent literature concerning the ability of the pulmonary vasculature to respond to these and other stimuli, and the possible location and mechanisms of the vasomotor response is reviewed.

Three types of heart-lung preparations are described which provide new degrees of experimental control. The use of continuous monitoring of many parameters is discussed and the experimental procedure is described. The use of pressure-flow curves as descriptive of changes in pulmonary vascular dynamics is discussed.

A statistical analysis of data obtained is presented and demonstrates significant reversible elevation of PAP and PA-LA in response to hypoxemia or acidemia, without significant elevations in LAP. Data is also presented which reveal that the interaction of these stimuli produces a greater elevation in PAP and PA-LA than occurs with either stimulus alone. Furthermore, it was demonstrated that increased sympathetic outflow resulting from CNS ischemia does not alter the pulmonary pressure-flow curves.

The validity of the methodology and results herein described are discussed with regard to the pertinent literature.

Table 6

FACTORS CONCEIVABLY INVOLVED IN A CHANGE IN PULMONARY VASCULAR RESISTANCE [45]

Mechanical (Passive)

Passive Cardiocirculatory Effects

1. Back pressure from left atrium or pulmonary veins
2. Change in pulmonary blood flow
3. Change in pulmonary blood volume
4. Bronchial collateral circulation
   a. Nutrition of nerves, ganglia and smooth muscle
   b. Patency of collateral circulation

Passive Respiratory Effects

1. Change in alveolar pressures
   a. Tone of bronchial smooth muscles
   b. Secretion of bronchial glands
   c. Alveolar surface tensions
2. Change in intrathoracic pressures
3. Tone of interstitial smooth muscle
4. Pericapillary edema

Vasomotor (Active)

Originating from without the lungs

1. Autonomic nervous system (including systemic chemoreceptors)
2. Catecholamines

Originating within the lungs

1. "Critical" closure of small muscular vessels
2. Intravascular chemoreceptors
3. Chemical stimuli (directly on vascular muscle)
4. Deranged vascular metabolism
5. Local reflexes

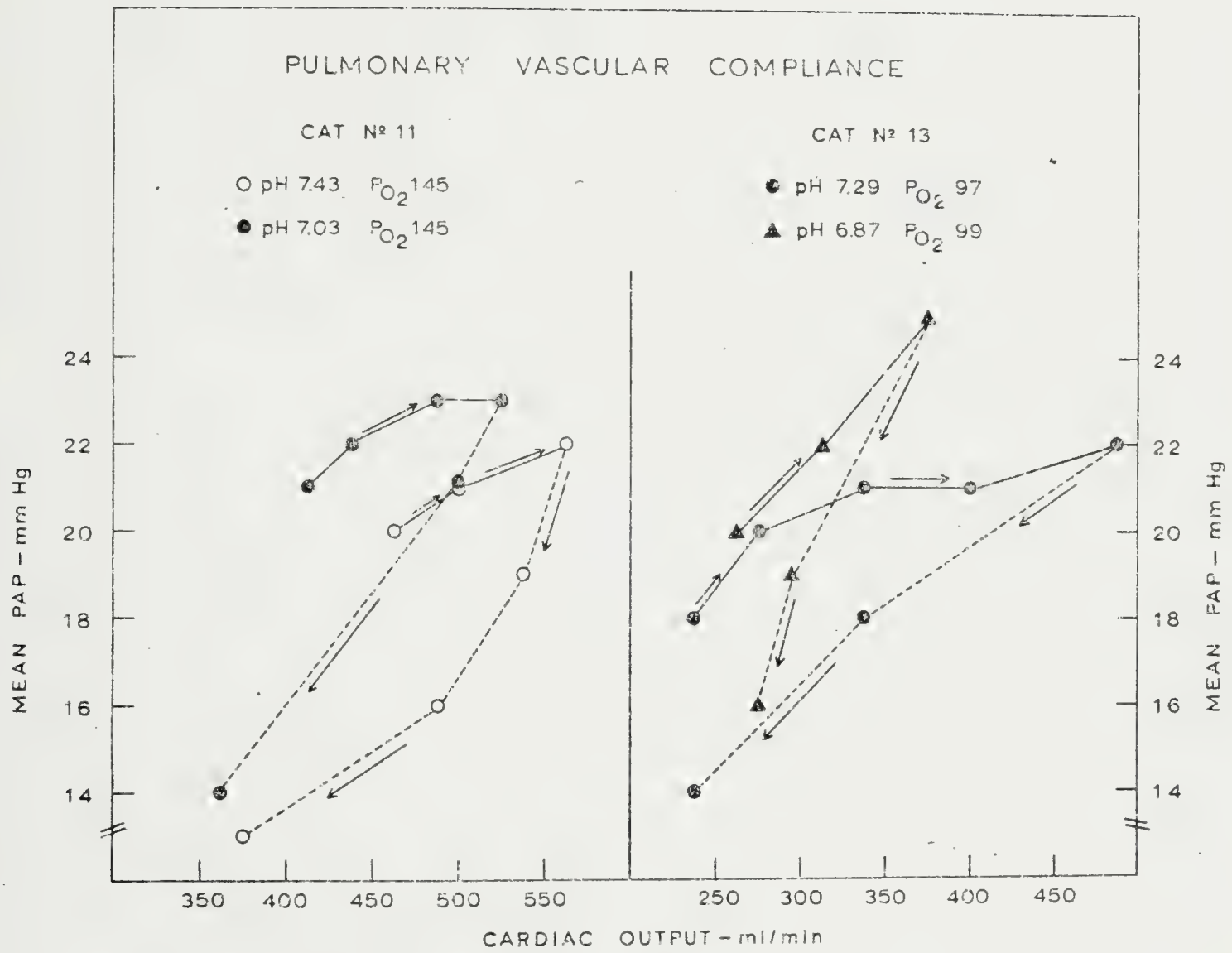

Fig. 23 Pulmonary vascular compliance curves obtained by the transfusion and hemorrhage of whole blood in a cat preparation. Solid lines represent transfusion; dotted lines represent hemorrhage. Of note, the entire compliance curve shifts toward the pressure axis in a graded fashion in response to acidemia.

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